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ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

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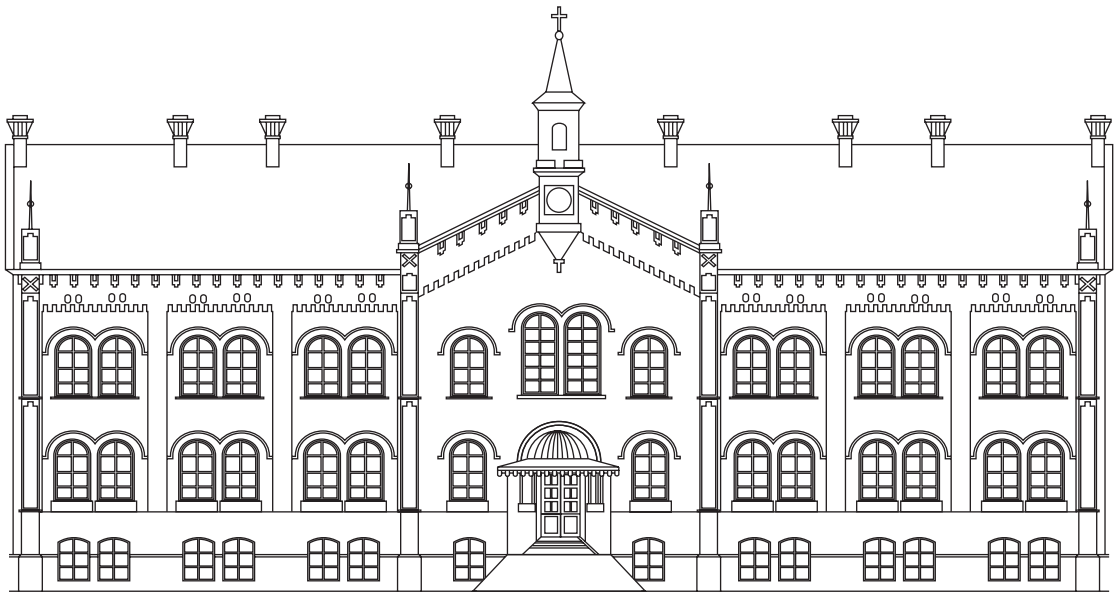

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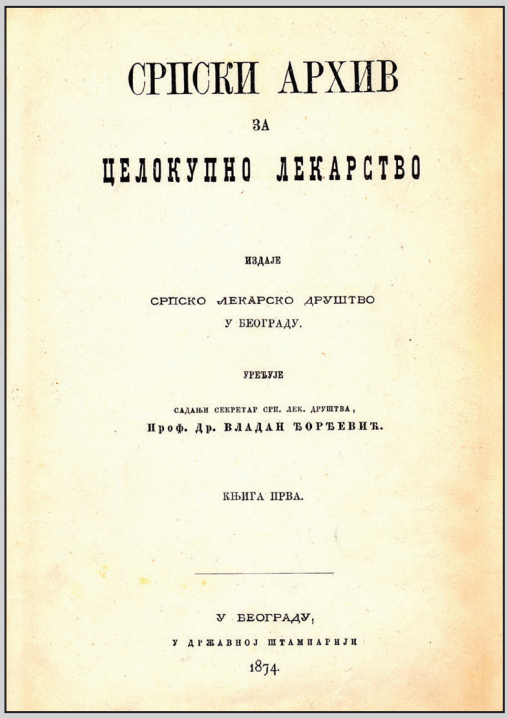


СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

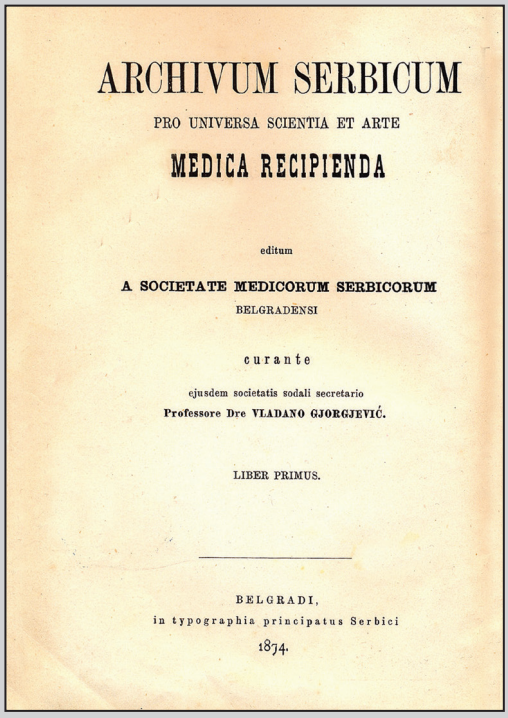
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основаног 1872. године, први пут штампан 1874. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Објављују се: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике и регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози.

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Поднесени рукопис подразумева да је његово публиковање одобрио одговорни ауторитет установе у којој је истраживање обављено. Издавач се неће сматрати правно одговорним у случају подношења било каквог захтева за компензацију. Треба да се наведу сви извори финансирања рада.

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Излази шест пута годишње

Српски архив за целокупно лекарство

ГОДИШТЕ 150. МАРТ–АПРИЛ 2022. СВЕСКА 3–4

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Оснивач, власник и издавач
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Председник
Академик Радоје Чоловић
Интернет страна: http://www.sld.org.rs

Адреса уредништва
Српски архив
Краљице Наталије 1, 11000 Београд, Србија
Телефон: +381 (0)11 409 27 76
+381 (0)11 409 44 79
Е-пошта: office@srpskiarhiv.rs
Интернет страна: www.srpskiarhiv.rs

Претплата и експедиција
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Телефон: +381(0)11 3245-149
Текући рачуни: 205-8041-21 и
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EDITORIAL OFFICE
Serbian Archives of Medicine
Kraljice Natalije 1, 11000 Belgrade, Serbia
Phone: +381 (0)11 409 27 76
+381 (0)11 409 44 79
E-mail: office@srpskiarhiv.rs
Website: www.srpskiarhiv.rs

SUBSCRIPTION AND DISTRIBUTION
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УВОДНИК ПО ПОЗИВУ / INVITED EDITORIAL

150 година Српског лекарског друштва

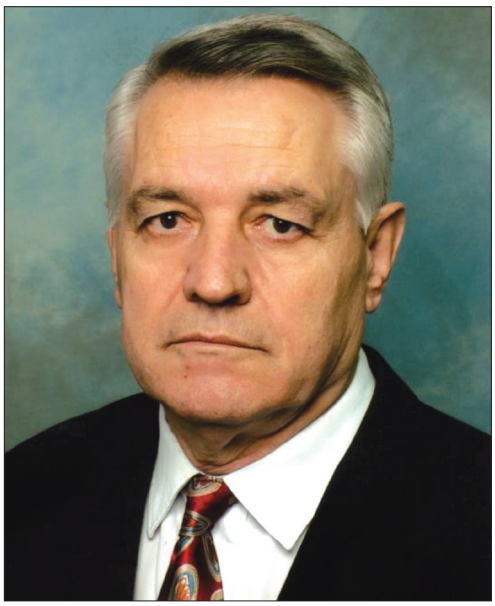
Академик проф. др Радоје Чоловић, председник Српског лекарског друштва

Четвртог маја 2022. године навршиће се 150 година од оснивања Српског лекарског друштва. То би и за један народ који је вековима живео у миру био догађај од изузетног националног значаја и разлог за понос и задовољство. У контексту тешке историје нашег народа, која као таква траје вековима, један овакав догађај има неупоредиво већи значај. Тако дугим трајањем и успешним радом Српско лекарско друштво постало је једним од најстаријих и највреднијих институција нашег народа и наше државе [1, 2]. Основано је 22. априла по старом (4. маја по новом) календару 1872. године, у веку у коме се после пропасти Првог српског устанка српски народ у Другом устанку, не само оружјем већ и мудрошћу и стрпљивошћу, најпре изборио да постане вазална кнежевима у оквиру Отоманског царства, па кад је у томе успео, њена тек настајућа интелигенција и њен народ почели су најпре да сањају пуну независност, а затим и обнову српске државе у њеним историјским границама.

Данас је тешко и замислити далековидост и одважност српских лекара да оснују Српско лекарско друштво у време кад је Србија имала само 63 лекара, од којих су седам били „магистри хирургије“ (лекарски помоћници) и један зубар, и кад су лекари пореклом из Србије могли да се изброје на прсте једне руке. Српско лекарско друштво је основано убрзо после, или чак пре лекарских друштава у неким напредним земљама Европе којима је трагична историја српског народа била нешто у шта су тешко уопште могли и поверовати.

Шта је др Владана Ђорђевића и неколико његових колега подстакло да и у таквим околностима оснују Српско лекарско друштво?

Све до последњих деценија 19. века узроци болести нису били познати. Мислило се да су заразне болести изазване „кужним испарењима“ из земље („мијазмама“). Смртност одојчади и мале деце била је огромна. Најчешћи узроци смрти биле су заразне болести. Од туберкулозе умирало је више од 40% одраслих. Венеричне болести, нарочито сифилис, биле су широко



Академик проф. др Радоје Чоловић, председник Српског лекарског друштва
Academician Prof. Radoje Čolović, the President of the Serbian Medical Society

распрострањење. Просечни животни век био је око 20 година. Особе од 30 до 35 година сматране су старим. Када би се појавиле епидемије куге, великих богиња или колере, дешавало се да умре трећина или половина становништва, посебно у градовима. Терапија је била неефикасна. Пуштање крви било је метод лечења скоро свих болести, чак и очигледних анемија. Уз пуштање крви често су коришћени еметици и пургативи. Нелечени болесници неретко су боље пролазили од лечених. Због непостојања анестезије било је могуће извођење само јако краткотрајних операција, и то са огромном смртношћу. Сматрало се да ране уопште не могу зарасти без гнојења, и да је важно само да се не прошири на ширу околину и цео организам, што је називано „еризипелом“, а данас је називамо сепсом, што је увек доводило до смрти.

Године 1846. откривена је општа, 1884. површинска, а 1892. локална инфилтративна анестезија, тако да је први пут у историји постало могуће извођење операција за које је било потребно време. Пастерово откриће да су голим оком невидљива бића узроци

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врења грожђа при производњи вина било је најава микробиологије. Са Листеровим (*Joseph Lister*) радовима (1867) у хирургији је започела ера антисепсе, а тек крајем 19. века асепса је почела да постаје стандардни поступак у хирургији. Открића појединих бактерија као узрочника болести снажно су подстакла развој хигијене и превентивне медицине.

У условима тако револуционарних промена, знања стечена на студијама медицине брзо су превазилажена. Лекари су новине у медицини морали ажурно пратити, што је подразумевало посећивање националних и међународних конгреса, набавку нових књига и стручних часописа. То је био врло захтеван посао, у којем су се једно време могли снаћи само најбољи и највреднији лекари. То је био посебно тежак задатак за лекаре практичаре, који су имали много посла а мало слободног времена. Тако се јавила прека потреба за оснивањем **лекарских друштава**, на чијим састанцима би лекари могли размењивати искуства из праксе и информације до којих су долазили из литературе. На тим састанцима су најбољи домаћи и страни лекари, често професори медицинских факултета, држали предавања о новим сазнањима, након којих су слушаоци постављали питања, износили своја запажања, обнављали стара и стицали нова знања. Лекарска друштва су оснивала **часописе**, у којима су штампана вредна искуства из праксе и најбоља саопштења са састанака друштва, резултати нових научних сазнања и оригиналних истраживања, изводи из одабраних радова из стране литературе, прегледни чланци, прикази нових књига, закључци са међународних конгреса, лекарски извештаји о стању здравља у појединим регионима и земљи у целини, и др. Лекарска друштва су оснивала **библиотеке** и **музеје** у којима су похрањивани ретки и поучни предмети и препарати на које су чланови друштва наилазили у пракси. У мањим земљама друштва су настојала да изучавају специфичности националне патологије и да стварају националну медицинску терминологију, а у народу су се борила против ризичних понашања, пушења, алкохолизма и проституције и промовисала личну, породичну и јавну хигијену.

То су били главни разлози који су подстакли др Владана Ђорђевића и другове да по угледу на напредне европске земље у којима су завршили медицинске факултете, и у тако крајње скромним околностима у којима се тада налазио српски санитет, оснују Српско лекарско друштво, „српско огњиште за науку" да „српску мисао позову на самостални културни рад" и да „зачну српску лекарску књижевност"

Српско лекарско друштво је основано по свим правилима како су оснивана лекарска друштва у најцивилизованијим земљама Европе, којима се ни данас ништа не би могло додати. **Устав** Друштва је до појединости дефинисао његове задатке и методе њиховог остваривања, прописао врсте састанака, одредио да Друштво има редовне, дописне и почасне чланове, међу које су бирани најславнији лекари Европе. Прописао је права и дужности чланова и часника Друштва који су бирани искључиво тајним гласањем на годишњим скуповима и то само ако је присутна надполовична већина редовних чланова. Друштво је било признато од званичних власти, имало је своје седиште и сталну адресу. Оно је на самом почетку основало свој **часопис** *Срйски архив за целокуйно лекарсшво,* који од тада редовно излази, **библиотеку,** зачело **музеј** и **фототеку**. Вредним и озбиљним радом Српско лекарско друштво је задобило поштовање власти, тако да су му часопис, оригинална дела српских лекара и преводи књига водећих страних лекара и професора медицинских факултета бесплатно штампани у Државној штампарији.

Српско лекарско друштво је све време пратило достигнућа медицинских наука и одмах их примењивало, бавило се стручним и научним усавршавањем својих чланова, радило на развоју и обогаћивању српске медицинске литературе, достојно представљало српску медицину у иностранству, радило на српској медицинској терминологији, на решавању најважнијих питања народне патологије, на унапређењу здравља народа, на промоцији медицинске науке у народу, промоцији личне, породичне и комуналне хигијене, на промоцији превентивне медицине и здравог начина живота. Борило се против алкохолизма, против надрилекарства, радило је на увођењу и усавршавању здравственог законодавства итд. Друштво као целина, а нарочито његови најистакнутији чланови, борили су се за оснивање Медицинског факултета, Министарства народног здравља и Лекарске коморе, а одмах после Другог светског рата и за оснивање Стоматолошког факултета.

Сходно тешким околностима кроз које је са својим народом и државом пролазило, Српско лекарско друштво је током једног и по века имало успоне и падове, успехе и неуспехе, али далеко више успеха него неуспеха. Његови чланови су све време волонтерски радили за добро свога народа и државе, **потпуно бесплатно**, **често и на сопствени трошак,** и путем посебног фонда помагали оболеле лекаре, лекарске удовице и лекарску сирочад.

Резимирајући рад Српског лекарског друштва током свечаног обележавања првих 50 година постојања Друштва, његов оснивач др Владан Ђорђевић изрекао је и ове речи:

„Српско лекарско друштво, не само да је потпуно остварило главну мисао својих оснивача, не само да је основало и развило српску лекарску књижевност и оснивало српску медицинску терминологију, него је још пре Универзитета и Краљевске Академије наука, створило једно српско огњиште за науку. Српско лекарско друштво непрекидно је ревносно пратило развијање целокупне медицинске науке и оних грана јестаственице, које су јој помоћнице, напредовало је са постепеним поступком лекарства, усавршавало се сопственим искуством, распростирало је то искуство писменим и усменим саопштењима, радило је на статистици разболевања у свим земљама у којима наш народ живи, и истраживало узроке тих болести, уколико су они у народним и географским особинама и

проучавало средства за уклањање тих узрока. Ни једна грана медицинских наука није остала недирнута и недискутована у Српском лекарском друштву". /.../ „Цео тај рад наштампан је у *Српском Архиву за целокупно лекарство* и у *Народном Здрављу*. Још веће су његове заслуге за државу".

Ђорђевић је закључио: „Кад се упореди рад Српског лекарског друштва са радом немачких лекара и природњака, може се слободно рећи да је наше Друштво за половину века стекло /.../ за наш народ исте заслуге које су немачки лекари и природњаци стекли за Германију".

Сто година после тих речи нашег оснивача, тешко је поверовати да је било које лекарско друштво у Европи за свој народ и своју државу учинило више него што је Српско лекарско друштво учинило за свој народ и своју земљу, поготово кад се на уму имају околности које нигде другде нису забележене а камоли да су се морале и преживети.

Слика 1. Дом Српског лекарског друштва. Задужбина др Стевана Милосављевића, првог Србина начелника Санитета. Снимљено 1934. године (из колекције г. Милоша Јуришића).
Figure 1. The home of the Serbian Medical Society. Endowment of Dr. Stevan Milosavljević, the first Serb who was the Chief of Medical Services. Taken in 1934 (from the private collection of Miloš Jurišić).

У својој 150 година дугој историји, Српско лекарско друштво је, на своју иницијативу и искључиво на сопствени трошак, непрекидно и несебично радило за добро свога народа и своје државе, све време делећи његову (често) трагичну судбину. Друштво је преживљавало трауматичне политичке догађаје, промену династије, шест ратова, од којих је **у Првом светском рату изгубило трећину чланова, што је јединствени случај у познатој историји света.** Српско лекарско друштво је прошло и кроз турбулентно време у заједничкој југословенској држави, и период комунистичке владавине, да би 1990. године ушло у вишепартијски систем, који му се за сва страдања и жртве које је поднело за добро народа и државе, 2000. године „захвалио" слањем тзв. „кризног штаба" састављеног од насилника у белим мантилима да га „ослободи" од оних који су за Друштво током тешких деведесетих година двадесетог века неуморно радили и успели да очувају све његове структуре, да одрже све његове активности, и да у крајњој оскудици очувају редовно излажење његова два главна часописа, *Српскоī архива за целокупно лекарство* и *Стоматолошкоī гласника*.

После пуних шездесет година подстанарског битисања, верни и одани чланови Српског лекарског друштва и њихове породице су му својим задужбинама и донацијама омогућили да 1932. године изгради свој сопствени Дом у центру Београда, на Зеленом венцу, у коме је по први пут имало сопствени амфитеатар за састанке, канцеларије за уредништво *Српскоī архива за целокупно лекарство*, просторије за музеј, канцеларије за чиновнике, неколико локала и 27 станова за издавање, који су му обезбеђивали изворе прихода, тако да је могло да купи и сопствену штампарију, чиме је решило вишедеценијски проблем ажурног штампања часописа и других издања Друштва (Слика 1). Српско лекарско друштво је деценијама примерно управљало вредним задужбинама лекара и лекарских породица које су му биле остављене на старање.

Сву ту имовину коју је Друштво стекло **без икакаве помоћи државе**, његову кућу („Дом Српског лекарског друштва, Задужбину др Стевана Милосављевића, првог Србина начелника санитета"), станове, плацеве, задужбине, и штампарију су му национализацијом одузеле комунистичке власти (Остављен му је на коришћење амфитеатар и на другом спрату неколико канцеларија за *Српски архив,* и администрацију, у којима је 1955. основан мали музеј). Ако се какво такво „разумевање" и објашњење за то злодело према Српском лекарском друштву може наћи у комунистичком догматизму, потпуно је неразумљиво и несхватљиво што тзв. „демократске власти" од 2000. године до дана данашњег одбијају и да разговарају да Српском лекарском друштву врате чак и отети му Дом, а камоли да му врате осталу имовину и задужбине лекара које су му биле предате на управљање и старање.

* * *

За илустрацију нечувене неправде која је национализацијом према лекарима задужбинарима и према Српском лекарском друштву учињена и чини се, наводимо главне делове задужбинског акта др Војислава М. Суботића, вишедеценијског секретара Српског лекарског друштва и Српског друштва црвеног крста, који је написао и потписао у јеку рата, 27. маја 1915. године, пет и по месеци након смрти сина јединца Луке Суботића и деветог дана након смрти супруге Меланије пл. Бајић. Иначе, Лука В. Суботић је завршио прву годину студија медицине у Инсбруку и од

првих дана балканских ратова и Првог светског рата био добровољац болничар, све време одбијајући било какве „привилегије“ које му је отац могао обезбедити. Његова мајка Меланија пл. Бајић, била је потомак породице Бајић која се из села Блаце из околине Битоља иселила у Аустрију са Арсенијем III Чарнојевићем. Породица је временом стигла у Беч и постала угледна и стекла статус „племенит“. Меланија Бајић Суботић је све време балканских ратова и Првог светског рата служила као преводилац у Српском друштву црвеног крста. Изузетно потресан, мало скраћен, **Задужбински акт др В. М. Суботића гласи:**

„Господину Министру Просвете и Црквених Послова

Смрћу мога јединца медицинара Луке, који је умро од трбушног тифуса 14. – 12. – 1914. год. који је добио вршећи добровољно службу лекарског помоћника у болничкој чети Дунавске Дивизије I позива, ја сам лишен родитељске земаљске среће.

Од превелике, неизмерне жалости за њиме, на дан 18. – 5. – 1915. год. у 8 и по часова престало је куцати срце његове мајке, а моје верне и дичне супруге госпође Меланије рођ. пл. Бајић, са којом сам се венчао у грчкој цркви у Бечу на Св. Луку 18. октобра 1892. год., и са којом сам све до њене смрти живео у најсрећнијем браку. Смрћу њеном ја сам лишен супружанске среће.

И њена и моја жеља је била да сачувамо и од заборава отргнемо име нашега јединца медицинара Луке.

Ја то хоћу да извршим на овај начин:

Хоћу да оснујем Задужбину не само под именом мога сина него и моје супруге. Како желим и после своје смрти, својим именом бити везан за њихова, мени тако драга и мила имена, то хоћу њиховој и својој Задужбини да дам наша сва три имена.

Име Задужбине гласиће:

ЗАДУЖБИНА МЕДИЦИНАРА ЛУКЕ
и његових родитеља
МЕЛАНИЈЕ И Д-Р ВОЈИСЛАВА М. СУБОТИЋА
И исписиваће се увек овако у три реда.

Испуњавам све прописе Закона о Задужбинама, и то:

1. Задужбину ову оснивам у циљу помагања сиротних лекара у Краљевини Србији, њихових удовица, и њихове сирочади, као и оних мајака лекарских, које су сироте, и које су живеле од помоћи својих синова лекара, па су њиховом смрћу или болешћу остале без помоћи.

Поред тога Задужбина ће служити и за помагање ограниченог броја ратне сирочади из сеоског и занатлијског сталежа у школовању за пољопривреду и занате.

Помоћ ће се указивати само српским поданицима, но без обзира на народност и религију.

2. У Задужбину ову уносим сва своја непокретна имања у која су уложени како сав мираз моје покојне супруге, тако и сва моја протекла зарада коју сам у току свога рада од 1. јула 1893. до смрти моје жене с њоме заједно штедећи сачувао и улагао у непокретна имања спремајући их за нашега јединца Луку.

Ово су моја непокретна имања:

а. – Кућа у Таковској улици Бр. 19. у Београду, сазидана 1899. год. без дугова. За њу сам до сада укупно утрошио 55.000 динара. Тапија овога имања гласи на мене и она носи број 5005 од 6. марта 1900. год. Првостепеног суда за варош Београд.

б. – По решењу истога Суда од 28. маја 1914. год. Бр. 22, 212 и Бр. 224. има се с тог имања скинути интабулација која стоји на имању. Решење није постало извршно због мобилизације и мораторијума.

б. – Празан плац код Фабрике дувана, ћоше испод апотеке, у Београду, купљен по тапији Првостепеног Суда за варош Београд од 28. септембра 1910. Бр. 34388., без терета, тада у вредности са узгредним трошковима свега 4000 Дин.

в. – Празан плац код железничке станице „Кланица“ у Београду до општинског рејона, купљен од г. Стеве Стевановића, чиновника Кланичног Друштва 12. септембра 1913. год. Овај је плац ограђен, велики је 2981 кв. мет. и купљен је за 30.000 дин. Остатак дуга Кланичком Друштву који сам примио куповином од г. Стевановића, износио је на дан 17. фебруара 1914. год. Дин. 6335.10, који се има исплатити, да би имање било без терета.

г. – Празан плац у Врњцима, по тапији Крушевачког Првостепеног Суда од 11. марта 1911. г. Бр. 10721., плаћен 7000 динара без терета.

д. – Празан плац у Ковиљачи, по тапији Лозничког Првостепеног Суда од 13. јуна 1914. г. Бр. 18592., плаћен 11000 дин., без терета.

Укупна вредност ових пет имања по куповној вредности у добу куповине, износи дакле 107.000 динара, која чини фонд ове Задужбине.

3. Овом ће Задужбином управљати Српско Лекарско Друштво, односно његов Управни Одбор под контролом само сваког годишњег скупа друштвеног. Управљање Задужбином вршиће се у смислу тачке под 1. овог задужбинског акта са овим додатком:

а. – Капитал Задужбине не сме се трошити, него само ¾ три четвртине, целокупног интереса, а једна четвртина да се уноси сваке године у капитал, у који ће се уносити и све неутрошене суме оне прве три четвртине интереса.

б. – Помоћ из Задужбине даваће се не само члановима Српског Лекарског Друштва, који су плаћали уредно своје чланске улоге како за друштво, тако и за садашњи друштвени фонд (по правилнику фонда у Срп. Архиву 1905. г. св. 11. стр. 517 и 518), него ће се помоћ издавати и оним лекарима, који нису били чланови С. Л. Д. Ово се односи и на њихове сиротне мајке, удовице и децу. Ово одређујем овако стога, што ме тако руководе обзири човечности и искуство стечено у ратовима 1912-13-14 и 1915. године. Ја желим дати доказа да ми на срцу подједнако лежи сва лекарска сиротиња, сва беда и несрећа њихова, без обзира на чланство и чланski улог, на народност и религију.

в. – Из прихода ове Задужбине биће дужно С. Л. Д. да сваке године помаже у изучавању пољопривреде и заната још по два сирочета погинулих ратника из сеоског и по два сирочета погинулих ратника из занатлијског сталежа и то у првом реду из парохије мога оца проте Милутина

(село Рамаћа, Угљаревац, Добрача, В. Шењ и М. Врбица), у другом реду из места рођења моје покојне мајке Марице (из Рудничке Горње Црнуће), у трећем реду из села Блаца битољског, одакле је пореклом породица моје покојне супруге Меланије пл. Бајић, а тек по том из целе Србије по најбољем нахођењу Управног одбора С. Л. Д.

Када не буде било ратне сирочади помагаће се друга сирочад у истом циљу и истим редом.

г. – Нарочито желим да Задужбина укаже помоћ сиротој лекарској деци за ниже и више школовање, и да обрати пажњу на то, да не морају сва лекарска деца постати лекари, него да се свако, према способности упути на изучавање подесних заната и трговине, како у Србији тако и у Иностранству.

д. – Српско. Лекарско Друштво биће дужно да сваке године изда на време о трошку Задужбине јевтин календар са поукама за народ и то не само о здрављу и болестима него и о свима другим потребама целог Српског Народа у најширем смислу речи. Радови ће се награђивати по нахођењу Управног Одбора С. Л. Д. из прихода Задужбине. То треба да буде најбољи српски календар и најкориснија књига за сваку српску кућу. С тога желим да се назове „Календар Српског Народа – Издање Суботићеве Задужбине." Ови ће бити од користи не само Српском Народу него ће од продаје Задужбини припасти леп приход и бити од велике моралне користи самом Лекарском Друштву. Чист приход од продаје овог календара има се уносити у капитал Задужбине.

ђ. – Задужбина ће водити засебан деловодни протокол и нарочито новчане књиге, тако да нема никакве административне ни новчане мешавине с осталом администрацијом и имовином С. Л. Д. и садашњег његовог фонда за лекарску сирочад.

* * *

/.../ Ја се обавезујем за време свога живота исплатити дуг са интересом Кланичком Друштву за плац код железничке станице „Кланица" у Београду, који је по обрачуну на дан 17. фебруара 1914. г. износио дин. 6.335.10. Ја сам још сада ово регулисао својим тестаментом, тако да се дуг исплати из мојих полица осигурања живота, ако бих ја умро пре него што бих стигао да извршим исплату овог дуга.

Српско Лекарско Друштво, односно његов Управни Одбор, овлашћујем да тек после рата изврши продају имања када буду повољне прилике за њихову продају; те да се добије што већа сума новаца за фонд Задужбине. /.../

Српско Лекарско Друштво, све док постоји, биће дужно, после моје смрти, старати се да се наша три гроба о трошку задужбине одржавају у реду.

На дан смрти мога јединца Луке, сваке године 14. децембра, велим да се одржи обична ванредна научна седница С. Л. Д. на којој ће председник само споменути да се она држи у спомен на његову прерану смрт. Дан моје смрти и дан смрти моје супруге не веже Друштво ни у ком погледу ни за какву обавезу према нама. Наше се име може само споменути уз име Лукино, када се одржи седница у његов спомен.

Желим да С. Л. Д., за наш спомен чува у својој сали наше три слике, и то тако да Лукина буде у средини. /.../.

* * *

Како Српско Лекарско Друштво потпада под Министарство Просвете и Црквених Послова, јер су његова правила потврђена од њега, то ми је част поднети Господину Министру ову своју одлуку о Задужбини, с молбом да Господин Министар изволи у смислу чл. 3 Закона о Задужбинама издејствовати највише одобрење за њено правно постојање.

27. маја 1915. год. Ниш — Д-р Војислав М. Суботић – млађи.

* * *

Сва имовина наведена у Задужбинском акту („без терета"), укључујући и кућу у Таковској 19, у којој су Суботићеви живели, продата је по тржишним ценама и новац је унет у Задужбину!.

Пошто и поред свих покушаја и напора (о чему у Друштву постоји потпуна документација) садашња Управа Српског лекарског друштва није успела да поврати ама баш ништа од национализацијом и узурпацијом отете му имовине и задужбина остављених му на старање, пред свим будућим руководиоцима Српског лекарског друштва стоји света обавеза **да не престану да се боре да се Друштву све отето врати, чиме би бар делом била исправљена нечувена историјска неправда која је њему и његовим задужбинарима нанета и даље се наноси, без икакве њихове кривице.**

Слика 2. Седиште Српског лекарског друштва од 1990. године (зграда бивше Болнице округа и вароши Београда изграђена 1868. године) у Видинској улици, данас улици Џорџа Вашингтона 19. У горњем левом углу кула са обновљеним сатом.
Figure 2. The headquarters of the Serbian Medical Society since 1990 (the building of the former hospital of the District and Town of Belgrade, built in 1868) at the former Vidinska street, nowadays Džordža Vašingtona 19. In the upper left corner is the photo of the clock tower.

* * *

Актуелна пандемија која улази у трећу годину задала је тежак ударац Српском лекарском друштву. Па ипак, Друштво у 151. годину улази у добром стању. Верујемо да будућност Српском лекарском друштву гарантују његово верно чланство, његових 65 специјалистичких секција које покривају све области и гране медицине, 56 подружница широм Србије, бројни активи и интерсекцијски одбори, Академија медицинских наука Српског лекарског друштва, *Српски архив за целокупно лекарство*, *Стоматолошки гласник*, и још око 20 часописа које издају Друштво лекара Војводине СЛД, Друштво лекара Косова и Метохије СЛД-а, подружнице и секције, изврстан музеј са сталном музејском поставком и више стотина акредитованих едукативних и научних програма које друштво држи сваке године, почев од редовних састанака, радионица, преко симпозијума, научних састанака и конгреса који су по правилу са међународним учешћем (Слика 2).

Припадници старијих генерација „активиста“ Српског лекарског друштва остају у нади да нове генерације чланова Српског лекарског друштва неће изневерити и разочарати др Владана Ђорђевића и његове колеге оснивaче, али и ни безбројне предане и вредне „раденике“ који су током 150 година, без икаквог личног интереса, у Друштву и за Друштво предано радили, за њега се борили и жртвовали на начине који су у постојећим околностима били могући, а које су сматрали најбољим и за Друштво најкориснијим.

Vivat, Crescat,
Floreat Societas Medicorum Serborum.

Сукоб интереса: Не постоји.

Председник Српског лекарског друштва
Академик проф. емеритус др Радоје Чоловић
Универзитет у Београду, Медицински факултет,
Београд, Србија
Српска академија наука и уметности, Београд,
Србија
E-mail: **r.b.colovic@gmail.com**

ЛИТЕРАТУРА

1. 150 година Српског лекарског друштва (ур. Р. Чоловић). Београд: Српско лекарско друштво, 2022.
2. Архива Српског лекарског друштва

150 Years of the Serbian Medical Society

Academician Prof. Radoje Čolović, the President of the Serbian Medical Society

May 4, 2022 marks the 150th anniversary of the founding of the Serbian Medical Society. For a nation, unlike ours, that has lived in peace for centuries, it would be an event of exceptional national significance and a reason for pride and satisfaction. In the context of difficult history of our people, which has lasted for centuries, such an event is incomparably more important. With such endurance and success, the Serbian Medical Society has become one of the oldest and most valuable institutions of our people and our state. It was founded on April 22, according to the Julian calendar (May 4, according to the Gregorian calendar) in 1872, during a century in which, after the failed First Serbian Uprising, the Serbs fought in the Second Uprising to become a vassal principality within the Ottoman Empire, and succeeded – not merely using weapons, but also with wisdom and patience. Upon triumphing, its newly forming wisdom and its people first started to dream of full independence, and henceforth of the restoration of the Serbian state within its historical borders. Today, it is difficult to imagine the foresight and courage of the Serbian doctors to establish the Serbian Medical Society at a time when Serbia had only 63 doctors, seven of whom were "masters of surgery" (medical assistants) and one dentist, all that at time when doctors of Serbian origin could be counted on the fingers of one hand. The Serbian Medical Society was founded soon after, or even before, medical associations in some advanced European countries for which the tragic history of the Serbian people was something they could hardly believe.
Keywords: Serbian Medical Society; 150th Anniversary; modern Serbian medicine

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Management of resources for orthopedic oncology and trauma patients during the COVID-19 pandemic – a retrospective cohort study

Burak Ozturan[1], Erhan Okay[1], Yavuz Yildiz[1], Yusuf Iyetin[2], Murat Demiroglu[1], Korhan Ozkan[3]

[1]SB Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Orthopedics and Traumatology Department, Istanbul, Turkey;
[2]Ozel Pendik Bolge Hospital, Orthopedics and Traumatology Department, Istanbul, Turkey;
[3]Istanbul Medeniyet University, Medical Faculty, Orthopedics and Traumatology Department, Istanbul, Turkey

SUMMARY

Introduction/Objective This study aims to evaluate changes in surgical strategy and orthopedic epidemiology, and to compare the frequency of surgeries before and during the COVID-19 pandemic.

Methods For periods from April 1 to May 31 in years 2019 and 2020, retrospective data on patient demographics and types of orthopedic surgical procedures were obtained from hospital databases in a tertiary referral hospital.

Results During the COVID-19 pandemic, the most common orthopedic surgical procedures performed were trauma surgery (n = 81), while other procedures were referred to oncology (n = 19), biopsy (n = 11), debridement (n = 10), amputation (n = 6), surgery of dysplastic hip (n = 5), and knee ligament repair (n = 1). The majority of trauma cases were hip fracture surgeries (n = 23). The mean age of the patients was 70.5 years. Sixty-three patients were female and 70 were male. Only one patient had a history of COVID-19 infection. In the same period during the year before the pandemic, 86 patients had trauma surgery, while 49 had oncological surgery and the mean patient's age was 54.5 years. Sixty-two patients in this group were female, and 73 were male. The number of tumor surgeries before the pandemic was higher compared to the same period during the pandemic ($p < 0.05$).

Conclusion During the pandemic, although all orthopedic surgeries decreased, the rate of osteoporotic hip fractures surgery was similar to that of the pre-pandemic state. This finding emphasizes the increased need to implement preventive measures regarding hip fractures during lockdown periods. The relation of hip and spine osteoporotic fractures surgery was not different before and during the pandemic.

Keywords: COVID-19; orthopedics oncology; trauma; surgery

INTRODUCTION

The new strain of coronavirus emerged in Wuhan, China in December 2019. Of unknown etiology, it primarily affects the respiratory system [1]. Widespread cases of pneumonia were reported in patients presenting at hospital and it seemed that linking them was the recent consumption of seafood or products from the city's live animal market [2]. This new disease was not completely unfamiliar but emerged as a novel mutation of the coronavirus. However, it was understood that this was much more contagious than the previously seen strains of this virus, namely severe acute respiratory syndrome (SARS), and Middle East respiratory failure syndrome (MERS) [1, 2].

Coronavirus is an RNA virus family that can affect many animal species and targets the respiratory tract. For unexplained reasons, mutations can occur and the virus can spread to humans [2].

On January 30, 2020, the World Health Organization announced the identification of this new type of coronavirus, then known as SARS CoV-2 [1]. As the virus spread to many countries, the World Health Organization declared a pandemic on March 11, 2020, and the disease was named COVID-19 [3]. Following the exponential spread of the disease, there was a change in hospital activities in all clinics, primarily in infectious diseases departments. Normal life came to a halt in many countries in Europe, which led to the need to change the distribution of the workforce within hospitals and to use resources more appropriately [4, 5].

Just as it was for all hospital departments, guidelines were issued to orthopedics and traumatology departments [6]. Elective cases were postponed, and surgical interventions were planned only for emergency cases that could not be delayed. The intention behind limiting the number of operations was to reduce the bed and manpower density across each hospital and protect both patients and healthcare personnel from infection [5]. In many countries all over the world, strict precautions were taken, including curfews, quarantines, and social distancing measures.

Although trauma cases reduced following the introduction of such precautions, a significant number of patients continued to present at their emergency departments with various

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Correspondence to:
Burak OZTURAN
SB Goztepe Prof. Dr. Suleyman Yalcin City Hospital
Orthopedic and Traumatology Department
Eğitim Mah. Dr. Erkin Cad.
34722 Kadikoy Istanbul
Turkey
ozturanb@gmail.com

fractures [7]. Even though orthopedics and traumatology clinics were not at the forefront in combating COVID-19 infections, they undertook a very important function in the treatment and planning of bone trauma along with the treatment of other patients requiring emergency treatment, especially bone / soft tissue infections and musculoskeletal system tumors [5]. Moreover, in many countries, orthopedists took on duties in other departments, most often in emergency departments or caring for infected patients on wards [4].

The aim of this study was to complete an epidemiological examination of patients treated in the Orthopedics and Traumatology Clinic during the pandemic, to evaluate the plans made during treatment, and to determine the changes in cases by looking at similar data from the same period in the year prior to the pandemic.

METHODS

The study included patients treated at the Orthopedics and Traumatology Clinic of Istanbul Medeniyet University Göztepe Training and Research Hospital, a tertiary level center, approved by the local institutional review board. A retrospective study included surgically treated patients at the Orthopedics and Traumatology Clinic between April 1 and May 31, 2020, when social restrictions were at their most intense, and these records were then compared to the records of patients treated in the same period of year 2019.

All patients who underwent surgery between April 1 and May 31, 2020 were included in the study. Those who underwent multiple operations were only included once, and, similarly, those operated on for multiple trauma in the same session were evaluated as single cases. All patients admitted to the ward were questioned about complaints including sore throat, fever, diarrhea, myalgia, and fatigue. Those with symptoms or suspicious findings on the preoperative pulmonary radiograph underwent a polymerase chain reaction (PCR) test preoperatively. Just one of the patients operated on (due to femoral neck fractures) had a history of COVID infection and their previous PCR test had been negative.

Only patients who had trauma and tumor surgery were included in the study for the period between April 1 and May 31, 2019. Elective cases and revision surgeries were excluded from the evaluation.

Trauma cases were separated into subgroups according to the bone or joint fracture. Tumor patients were classified as either benign or malignant.

Data from the study were analyzed statistically using NCSS 2007 software (Number Cruncher Statistical System, Kaysville, UT, USA). To determine the relations between qualitative data, the χ^2 test and Fisher's exact test were used, for $p < 0.05$ level of significance.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

In April and May 2020 during the COVID-19 pandemic, a total of 133 patients had surgery at our clinic, comprising 70 males and 63 females, with a mean age of 70.5 years. The main reasons for surgery were trauma in 81 cases and tumor in 19. There were 10 debridements, 11 biopsies, six amputations, five pediatric interventions, and one patient had surgery for a sports injury (Table 1). Of the 19 tumor cases, 14 were malignant and five were benign. The benign tumor diagnoses included intraosseous lipoma in one case with severe pain, a simple bone cyst in one case and an aneurysmal bone cyst in one case (both with a risk of fracture), a giant cell localized tumor in one case, and a fibro-osseous pseudotumor of the skin in one case. In 10 patients with ongoing infection treatment started before the pandemic, debridement was planned in this period because the infection had progressed or recurred, and these patients underwent debridement more than once in this period. The treatment of five pediatric patients for developmental dysplasia of the hip was continued in this period as the treatment had already been started or there was a risk of missing the treatment window. Amputation was performed on five patients as diabetic feet had disrupted circulation, which was threatening their general condition, and amputation of the upper extremity at the proximal humerus level was made in one case secondary to trauma. Open or closed diagnostic biopsy was performed on 11 patients with a tumor thought to be clinically aggressive. Repair of the medial collateral ligament was applied in the case with a sports injury.

Table 1. Surgeries performed at our clinic during the COVID-19 pandemic

Surgeries	April–May 2019	April–May 2020
Fractures	86 (47%)	81 (61%)
Amputations	7 (4%)	6 (5%)
Biopsies	6 (3%)	11 (8%)
Malign tumors	21 (12%)	14 (11%)
Benign tumors	28 (16%)	5 (4%)
Pediatrics	2 (1%)	5 (4%)
Sports injuries	15 (8%)	1 (1%)
Debridements	17 (9%)	10 (8%)

The majority of the trauma surgery during the pandemic were performed for hip fractures. Of the 81 trauma patients, 23 were hip fractures, comprising nine femoral neck fractures and 14 trochanteric femoral fractures. A total of nine spine fracture surgeries were performed in this period, three of which were pathological.

During the months of April and May 2019, the year prior to the pandemic, a total of 135 patients had surgery at our clinic due to trauma or tumor, comprising 73 males and 62 females, with a mean age of 54.5 years. There were 86 trauma and 49 tumor-related cases. Of the hip fracture patients in year 2019, 17 had a femoral neck fracture and 15 had a trochanteric fracture. In this period, six patients had surgery for spine fracture (Table 2). We had also performed seven amputations unrelated to tumoral conditions, six

biopsies, surgeries relating two developmental dysplasia of the hip, 15 sports trauma injuries (anterior cruciate ligament ruptures and meniscal tears), and 17 debridements in this period. Of the 49 patients having tumor surgery in the year before the pandemic, the tumor was malignant in 21 patients and benign in 28 patients (Table 3).

Table 2. Comparison of fracture distribution during the pandemic lockdown and before the pandemic

Fracture type	April–May 2019	April–May 2020	p
Hip	32 (37%)	23 (28%)	0.226*
Elbow	2 (2%)	12 (15%)	0.004*
Hand and wrist	14 (16%)	12 (15%)	0.794*
Foot and ankle	8 (10%)	7 (9%)	0.881*
Shoulder	6 (7%)	/	/
Periprosthetic	1 (1%)	2 (2%)	0.612**
Mid-shaft	8 (10%)	11 (14%)	0.384*
Knee	7 (8%)	5 (6%)	0.623*
Pelvis	2 (2%)	/	/
Spine	6 (7%)	9 (11%)	0.350*
Total	86	81	

*χ^2 test;
**Fisher's exact test

Table 3. Influence of the COVID-19 pandemic on the number of malign and benign tumor surgeries

Tumor	April–May 2019	April–May 2020	p
Malign	21 (43%)	14 (74%)	0.022*
Benign	28 (57%)	5 (26%)	

*χ^2 test

Surgeries performed during the pandemic were in 61% related to trauma, and in 15% related to tumor. The rates of other surgeries are presented in Table 1. In trauma surgery, the rate of hip fractures was 28% during the pandemic and 37% in the corresponding period in 2019. The rate of spine fracture surgery was 11% during the pandemic and 7% in the corresponding period in 2019. No significant difference was determined between the two periods regarding hip–spine relation in trauma surgery ($p > 0.05$) (Table 4).

Table 4. Influence of the COVID-19 pandemic on the number of hip trauma and spine trauma surgeries

Trauma	April–May 2019	April–May 2020	p
Hip	32 (84%)	23 (72%)	0.237*
Spine	6 (16%)	9 (28%)	

*χ^2 test

Of the malignant tumor surgical treatment, 14 patients had surgery during the pandemic and 21 patients had surgery in the corresponding period in 2019. Malignant tumor surgery frequency was lower during the pandemic than in the same two-month period of the previous year ($p < 0.05$). Of the benign tumor surgeries, five patients had surgery during the pandemic, which is significantly lower than 28 patients in the corresponding period of the year 2019 ($p < 0.05$) (Table 3).

DISCUSSION

When compared with the corresponding period in the previous year, the trauma surgery frequencies (number of cases) in years 2019 and 2020 were generally similar despite the curfew (state of emergency) due to the COVID-19 pandemic. The majority of surgeries during the pandemic were related to the treatment of fractures as a result of osteoporosis. In addition to the mean age of all patients being 70.5 years, the rate of trauma patients with osteoporotic hip or spine fracture was 39% of the total number of patients indicating that elderly patients are present at orthopedics and traumatology clinics even in periods of pandemic. Even though difference in hip fractures surgery rates was not statistically significant between years 2019 and 2020, this difference would be approved as significant if the number of cases were higher.

It has been scientifically shown that the elderly infected with COVID-19 have a more severe course and higher mortality rates than young and middle-aged patients. COVID-19 is also more severe and more often fatal in those with comorbidities than in healthy individuals [8]. In light of this knowledge, another important point is that a prolonged preoperative preparation period for patients presenting at hospital with a hip fracture could be a cause of increased mortality rates, due to higher risk of COVID-19 infection [9, 10].

Even if they are not working on the front-line of the infection, it must be taken into consideration that as orthopedists are working in many areas at risk within the hospital, they may become asymptomatic carriers of the disease, able to spread it to patients. Likewise, if ward patients who are not suspected of having the virus do not wear a mask, they constitute a great risk to doctors, nurses, and auxiliary healthcare workers, as they may be asymptomatic carriers too [11].

Lockdown did not change the relation between different osteoporotic fracture types, such as hip fractures and spine fractures, in surgical practice. Almost all elderly patients who had hip or spine fracture surgery had been brought to the Emergency Department after a fall at home. Therefore, it could be concluded that if the elderly spend most of their time at home, it will not favorize any of these osteoporotic fracture types. During the pandemic, only four patients underwent surgery following a traffic accident.

Precautions to prevent falls at home are always important but are often not given sufficient attention. Falls at home can be reduced for the elderly with simple precautions [12]. This prevention is especially important during the COVID-19 pandemic, due to the lack of hospital resources.

Generally, as the warmer weather starts in April, people start to spend more time outdoors, and there is a corresponding increase in upper extremity trauma, but it starts to decrease in autumn [13]. However, there had been reported that the pandemic lockdown caused an increase in upper extremity trauma, as elderly people were home alone and unable to call caregivers due to restrictions, trying to perform tasks on their own [14]. Despite the pandemic

period and the quarantine of the elderly at home during April, the predicted increase in upper extremity trauma cases was not recorded at our clinic except for elbow fractures, being in accordance with Colen et al. [13].

Bone and adjacent soft tissue tumors are followed by severe morbidity and risk of mortality; thus, their treatment should not be neglected. It is very important for these patients to receive appropriate, timely adjusted treatment, as delayed or inappropriate treatment may be life-threatening [15, 16]. In our study, 11 biopsies were performed during the pandemic about 8% of all cases. As an oncological diagnosis can be late due to the late biopsy, these interventions were performed during the COVID-19 pandemic, to provide the start of oncological therapy on time. Tumor cases accounted for about 15% of all the cases from this study during the pandemic, and 74% of them were malignant tumors. While 14 cases with malignant tumor underwent surgery during the pandemic, 21 cases with malignant tumor had surgery in the corresponding period of the previous year. This could be explained by patients' assumption that they would not be able to see a doctor because of the pandemic and/or by their fear to come to hospital due to the risk of infection.

Benign bone tumors and cysts are very common. These tumors can cause local pain and local weakness of the bone, increasing the risk of fracture [17]. Benign bone and adjacent soft tissue tumors accounted for about 4% of all surgeries at our clinic during the pandemic. Three of these patients were thought to be at high risk of fracture, and two patients were suffering with pain. Although benign tumors are generally more common than malignant tumors, we operated on more malignant tumor cases than benign ones during the COVID-19 pandemic lockdown period. Most of the benign tumor cases were probably canceled due to the milder symptoms without the need for urgent treatment.

Ulcers in the foot are presented as the complication of the diabetes in approximately 10–15% of diabetic patients [18]. About 20% of diabetic ulcers result in amputation [19]. COVID-19 has a more severe course in patients with hypertension and vascular disease and especially in those with diabetes [20]. Therefore, a team specialized in diabetic ulcers must always be prepared, the patients must be evaluated carefully and eventual surgery has to be performed as soon as possible [21]. During the pandemic, amputation was performed on five patients with diabetic foot, thus reduced physical activity was confirmed as a risk factor for such diabetic complication.

Throughout the COVID-19 pandemic, just as for all branches in the hospital, the Orthopedics and Traumatology Clinic was affected. In addition to reduced operation capacity in operating theatres, due to the reassignment of doctors and other personnel, elective cases were cancelled, and only emergency cases were operated on, with the aim of reducing the spread of the disease [22]. In the USA, the number of primary arthroplasty patients postponed for one week was approximately 30,000, while the number of revision cases was approximately 3,000. Thus, the planning of surgery for these patients again after the pandemic with the addition of new patients puts great pressure on healthcare systems [23]. Throughout the months of April and May, the specialists and residents from our clinic also served in the hospital's COVID wards. Planning for the elective surgery cases was postponed during the pandemic.

New methods should be considered to reach doctors as a result of postponed patient treatments. The use of telemedicine systems, which was known and used by orthopedic doctors and patients before the pandemic, increased during the pandemic period [24]. It has been noted in studies that there is no difference in patients' satisfaction between telemedicine and face-to-face examination [25, 26]. We still believe that face-to-face examinations are more successful and reduce complication rates more efficiently than telemedicine, and so we do not have any current plans to use telemedicine in the future.

To evaluate organizational difficulties caused by the COVID-19 pandemic, and to plan for similar outbreaks in the future, there is a need for multicenter studies with greater numbers of patients.

CONCLUSION

Although many areas of normal life came to a halt during the pandemic, causing a reduction in the number of patients coming to a hospital, the need for hospital treatment was still present. At our orthopedic department, these patients were predominantly with fractures and musculoskeletal tumors. The lockdown did not change the relation between different osteoporotic fracture types, such as spine and hip fractures, comparing COVID-19 lockdown period and the same calendar period in the previous year, without pandemic. Compared to the same calendar period for year 2019, the number of surgically treated malignant tumor cases was greater than that of benign tumors in 2020, possibly due to patients withdrawing from treatment related to benign bone tumors during the COVID-19 period. Difficulties in reaching hospital and a lack of organization to make sufficient interventions for patients can cause a delay in the treatment of some life-threatening diseases. Therefore, while there were collective restrictions during the pandemic, hospitals should adapt its organization to provide the continuation of some necessary treatments. Implementation of precaution measures and adequate organization of hospital service can help to avoid the progression of some disorders and to ensure better resource handling in orthopedics and traumatology departments in any future pandemics or disaster situations.

Conflict of ınterest: None declared.

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Управљање ресурсима за ортопедску онкологију и болеснике са траумом током пандемије ковида 19 – ретроспективна кохортна студија

Бурак Озтуран[1], Ерхан Окај[1], Јавуз Јилдиз[1], Јусуф Ијетин[2], Мурат Демироглу[1], Корхан Озкан[3]

[1]Гозтепска градска болница „Проф. др Сулејман Јалчин", Одељење за ортопедију и трауматологију, Истанбул, Турска;
[2]Болница округа Пендик, Одељење за ортопедију и трауматологију, Истанбул, Турска;
[3]Истанбулски универзитет „Меденијет", Медицински факултет, Катедра за ортопедију и трауматологију, Истанбул, Турска

САЖЕТАК

Увод/Циљ Циљ ове студије је процена организационих и епидемиолошких промена у ортопедској хирургији, као и упоређивање потреба за различитим хируршким интервенцијама пре и током пандемије ковида 19.

Методе Ретроспективно су анализирани демографски подаци и подаци о заступљености хируршких интервенција, добијени у терцијарној здравственој установи, за период од 1. априла до 31. маја у 2019. и у 2020. години.

Резултати У наведеном календарском периоду током пандемије ковида 19 (у 2020. години) највећи број хируршких интервенција се односио на збрињавање прелома ($n = 81$), док су се остале интервенције односиле на збрињавање онколошких стања ($n = 19$), биопсију ($n = 11$), дебридман ($n = 10$), ампутацију ($n = 6$), операцију диспластичних кукова ($n = 5$) и лигаментарну репарацију колена ($n = 1$). Највећи удео трауме су чинили преломи кука ($n = 23$). Просечна старост болесника је била 70,5 година, а полну структуру су чиниле 63 жене и 70 мушкараца. Само један болесник је имао историју инфекције ковидом 19. У години пре пандемије (2019. год.) у истом је календарском периоду оперисано 86 болесника због трауме и 49 болесника због онколошког стања. Просечна старост болесника је била 54,5 година, а полну структуру су чиниле 62 жене и 73 мушкараца. Уочено је да је заступљеност онколошких интервенција била значајно већа у 2019. год. ($p < 0,05$).

Закључак Док је укупан број ортопедских операција био у паду током пандемије, укупан број оперативно збринутих остеопоротичних прелома кука се није значајно смањио. Ово упућује на потребу за предузимањем мера усмерених на превенцију прелома кука током кућне изолације становништва. Однос хируршки збринутих остеопоротичних прелома кука и кичме у периоду пандемије се није разликовао у односу на период пре пандемије.

Кључне речи: ковид 19; онколошка ортопедија; траума; хирургија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effect of orthodontic extrusion on alveolar bone – a prospective clinical study

Ivan Arsić[1], Nemanja Marinković[1], Miroslav Dragović[2], Dejan Stamenković[3], Zorana Stamenković[1], Nenad Nedeljković[1]

[1]University of Belgrade, School of Dental Medicine, Clinic for Orthodontics, Belgrade, Serbia;
[2]University of Belgrade, School of Dental Medicine, Department of Medical Statistics and Informatics, Belgrade, Serbia;
[3]University of Belgrade, School of Dental Medicine, Department for Prosthetics, Belgrade, Serbia

SUMMARY

Introduction/Objective Orthodontic extrusion is the procedure for moving the teeth in a vertical, coronal direction. This movement induces changes in the periodontal ligament and the production of new alveolar bone.

The objective of the study was to determine the changes on buccal, palatal and interdental alveolar bone as a result of orthodontic extrusion.

Methods Experimental group included six patients who received orthodontic treatment with the fixed appliances; the control group included four patients without orthodontic treatment. Two cone-beam computed tomography scans (initial and final) were obtained for each patient in both groups. Length of a tooth, shortest distance from tooth's center of resistance to the referent plane, distance from buccal or palatal plate tip to the enamel-cement junction, the height of interdental septum, buccal and palatal plate vertical gain, buccal and palatal plate thicknesses were measured on initial and final scan in the experimental and control group.

Results The reduced length of the extruded tooth was observed in the experimental group. The distance from buccal and palatal plate tip to the enamel-cement junction, mesial interproximal bone septum and buccal plate gain significantly increased in the experimental group. No significant difference was found in the distal interproximal bone septum, palatal plate gain and buccal/palatal plate thickness between groups.

Conclusion Orthodontic extrusion affects alveolar bone level by gaining the hard tissue buccal and mesial of extruded teeth, while buccal and palatal plate thickness insignificantly changed.

Keywords: orthodontic extrusion; alveolar bone level; CBCT

INTRODUCTION

Orthodontic extrusion (OE) is an orthodontic procedure used for moving the teeth in vertical coronal direction [1]. OE is also known as forced extrusion or forced tooth eruption. It can be achieved with various orthodontic appliances. However, the most effective OE is provided with the use of fixed orthodontic appliance [1]. During the stage of alignment, in the straight wire technique, extrusive forces are often present, especially in the brackets of vertically displaced teeth [2]. Straight wire fixed appliance, in an early stage of treatment, produces light vertically directed forces with the use of thin Ni-Ti arches [3].

There are many evidences regarding the tooth movement and its effect on surrounding alveolar bone and periodontal soft tissue. Extrusive tooth movement induces changes in the periodontal ligament, triggers the osteoblastic activity which includes the production of new bone and soft tissue growth [4]. Treatment of missing teeth, with the alveolar ridge resorption, often requires multidisciplinary approach. Orthodontic tooth movement affects the surrounding periodontal tissue, depending on the direction of the orthodontic force application [5].

Before insertion of a dental implant, OE (slow extraction) of the tooth with poor prognosis is indicated for producing sufficient new bone and increasing the height of the alveolar ridge [6, 7]. This procedure is named Implant Site Development (ISD). Some authors state that it is necessary to augment soft and hard periodontal tissue before dental implant planning [8, 9].

OE provides coronal movement of the tooth, thus stretching periodontal fibers and initiating osteoblastic activity. Fibroblasts differentiate into osteoblasts and the production of new bone begins [2]. This effect of OE may also be used in decreasing the depth of an isolated periodontal pocket [3]. OE indications are classified into four different categories: 1. Orthodontic indications (vertically displaced, infraocclusal teeth, impacted teeth, dentoalveolar open bite, traumatically intruded teeth) [10, 11]; 2. Restorative and prosthetic indications (subcrestal dental caries or oblique/transversal fractures) [12, 13]; 3. Periodontal indications (vertical and/or angular infrabony pockets,

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Correspondence to:
Nemanja MARINKOVIĆ
Gastona Gravijea 2
11000 Belgrade
Serbia
nemanja.marinkovic@stomf.bg.ac.rs

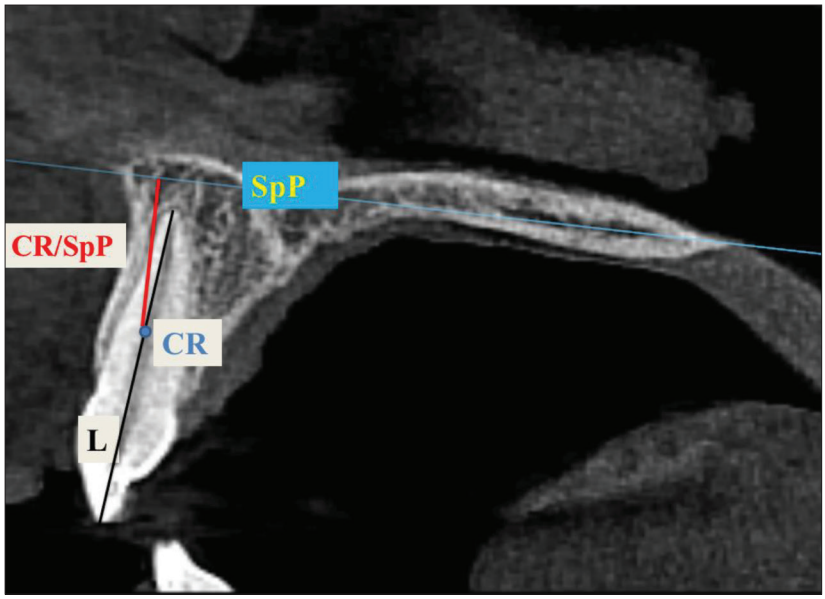

Figure 1. Cone-beam computed tomography scan with dental and skeletal measurements; SpP – maxillary plane; CR – center of resistance of the tooth; L – tooth length; CR/SpP – vertical distance of the center of resistance of the tooth to maxillary plane

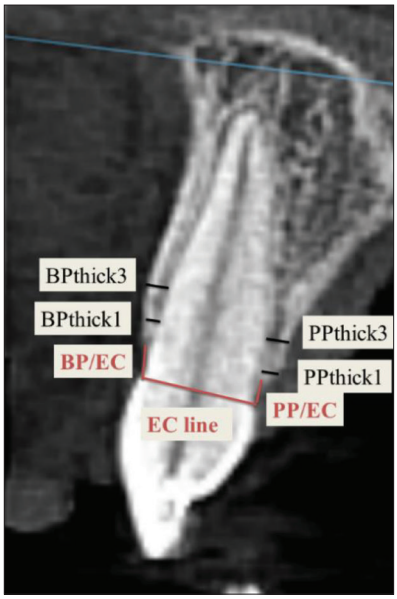

Figure 2. Cone-beam computed tomography measurements of buccal and palatal plate height and width; BP – buccal plate; PP – palatal plate; thick1/thick3 – thickness of buccal and palatal plate measured 1 mm/3 mm from the tip of the alveolar crest; BP/EC – distance from the tip of buccal plate to enamel-cement junction; PP/EC – distance from the tip of palatal plate to enamel-cement junction; EC line – enamel-cement junction line

papilla height reduction, inadequate gingival margin position) [14, 15]; 4. Implant Site Development, prior to dental implant insertion [16].

OE improves the quality and structure of attached gingiva and alveolar bone, esthetics and dental implant osseointegration, both in anterior and posterior region [17].

The aim of this study was to determine the changes on buccal, palatal and interdental alveolar bone as a result of OE.

METHODS

The study initially included 22 patients who referred to University of Belgrade, School of Dental Medicine, Department of Orthodontics, for orthodontic treatment. Inclusion criteria (age above 19 years, with diagnosed vertically displaced teeth, infraocclusal frontal teeth and/or dental open bite) were met by all included participants. We excluded 12 patients from this study, based on exclusion criteria (endodontic treatment of extruded teeth during orthodontic treatment, previous orthodontic treatment, poor oral hygiene and periodontal health, smoking habit, presence of systemic diseases). Finally, this study included 10 participants (four male, six female).

Patients were divided into two groups. The first group (experimental) included six patients (three male, three female) who received orthodontic treatment with fixed orthodontic appliance (straight wire technique, Ricketts's prescription, slot 0.018"). Orthodontic treatment with the extraction of four first premolars was performed in 4 cases. Two cone-beam computed tomography (CBCT) scans were obtained for each patient in the region of the tooth with indicated OE (total of 11 teeth), initial before the treatment and final at least six months after OE. CBCT scans were obtained with Soredex 3D SCANORA system (Soredex, Tuusula, Finland), in high-resolution (voxel size 0.1 × 0.1 × 0.1 mm) in M field of view (80 × 100 mm), in both groups. The Ethics Committee approved this prospective study (no. 36/4), which was also performed in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

The second group (control) included four patients (one male, three female). Two CBCT scans were obtained for each patient in the region of upper anterior teeth (total of 13 teeth). The final scan followed the initial after at least 14 months. These patients were not orthodontically treated between initial and final CBCT scan.

A period of time between initial and final CBCT scan for each patient is presented as ΔT value.

On CBCT's, following parameters were measured (OnDemand3D Project Viewer Limited Database, version 1.0.0.1, Cybermed, Seoul, South Korea):

L presents length of the tooth in sagittal projection.

CR/SpP and CR/MP presents shortest distance from center of resistance (CR) of the tooth to maxillary (SpP) or mandibular plane (MP). SpP (maxillary plane) was marked as a plane orthogonal to sagittal plane, connecting anterior and posterior nasal spine. MP was marked between the contact point of mandibular symphysis and corpus anteriorly and the lowest point of mandibular angle posteriorly. Vertical movement (VM) of the tooth was presented as the difference between final and initial value (ΔCR/SpP or ΔCR/MP). CR was marked as a point on tooth axis in sagittal projection, between coronal and middle third of the root of the tooth, measured from alveolar crest to the apex of the root (Figure 1) [18].

BP/EC and PP/EC presents distance from buccal (BP) or palatal plate (PP) tip to enamel cement junction (EC). Changes in BP and PP height were presented as the difference of measured final and initial values, correlated with the vertical movement of the tooth (Figure 2).

BP vertical gain (BPgain) and PP vertical gain (PPgain), were calculated using the following formula: BPgain = VM – ΔBP/EC and PPgain = VM – ΔPP/EC.

The difference between final and initial measurement value is presented as Δ.

As shown in Figure 2, BP and PP thicknesses were measured on two levels, 1 mm (BPthick1 and PPthick1) and 3 mm (BPthick3 and PPthick3) from the tip of BP or PP.

The height of interdental septum (IS) was measured from its tip to maxillary or MP, both mesial and distal of the tooth (ISmesial and ISdistal).

All statistical analyses were done using Statistical Package for Social Science (SPSS software package, version 26.0; IBM Corp., Armonk, NY, USA). Mean and standard deviation (SD) were used description of numeric data. Numeric data were analyzed using Independent T – Test and Mann–Whitney U test according to p values obtained by One-Sample Kolmogorov–Smirnov test for normal distribution. Univariate and multivariate linear regression models were used to assess the relationship between parameters. Dependent variable was vertical tooth movement while other relevant observed parameters were used as explanatory variables. Differences were considered significant when the p value was ≤ 0.05.

The reliability of the measurements was assessed by means of Intraclass Correlation Coefficient (ICC). Calculations of the ICC were done using a single measurement, absolute agreement, two-way mixed model according to guidelines for the ICC model selection proposed by Koo and Li [19]. ICC calculations were done using IBM SPSS Software package for every variable measured at two points in time. After getting the values for the ICC, standard error of measurement (SE m was calculated using following formula: SE m =SD*$\sqrt{(1-ICC)}$).

RESULTS

The mean ages of participants in experimental and control group were 23.91 ± 4.67 years and 22.23 ± 1.69 years, respectively. The difference between the mean ages of both group participants was not considered to be statistically significant, according to the Mann-Whitney U test (p = 0.791).

Mean time interval between initial and final CBCT scan in experimental (4.09 ± 2.63 years), and control group (3.04 ± 2.12 years) did not differ significantly.

A total of 24 teeth from 10 patients was investigated. The differences between final and initial measurements in both groups are presented in Table 1.

Table 1. Cone-beam computed tomography measurements of dental and skeletal parameters: difference of final and initial parameter values in both groups

Parameter	Experimental group $\bar{X}$± SD	Control group $\bar{X}$± SD	Significance
ΔL (mm)	−1.30 ± 0.84	0.04 ± 0.06	[2]0.000*
VM (mm)	1.52 ± 1.32	0.11 ± 0.09	[2]0.000*
ΔBP/EC (mm)	−0.66 ± 0.48	−0.07 ± 0.41	[1]0.004*
ΔPP/EC (mm)	−1.11 ± 1.13	−0.15 ± 0.27	[2]0.004*
ΔBPthick1 (mm)	−0.02 ± 0.37	0.03 ± 0.09	[2]0.706
ΔBPthick3 (mm)	0.16 ± 0.37	0.07 ± 0.20	[2]0.908
ΔPPthick1 (mm)	0.06 ± 0.44	−0.05 ± 0.15	[1]0.397
ΔPPthick3 (mm)	0.22 ± 0.82	−0.13 ± 0.38	[2]0.622
ΔISmesial (mm)	1.35 ± 1.59	−0.03 ± 0.60	[1]0.008*
ΔISdistal (mm)	0.27 ± 1.57	0.00 ± 0.55	[1]0.573
BPgain (mm)	0.85 ± 1.14	0.03 ± 0.43	[2]0.002*
PPgain (mm)	0.40 ± 1.79	−0.05 ± 0.27	[2]0.077

Δ – difference between two measurements; L – length of the tooth in sagittal projection; VM – vertical movement; BP/EC – buccal plate tip to enamel cement junction; PP/EC – palatal plate tip to enamel cement junction; BPthick1 – buccal plate thickness on 1 mm level; BPthick3 – buccal plate thickness on 3 mm level; PPthick1 – palatal plate thickness on 1 mm level; PPthick3 – plate thickness on 3 mm level; ISmesial – height of interdental septum measured from its tip to maxillary or mandibular plane, mesial of the tooth; ISdistal – height of interdental septum measured from its tip to maxillary or mandibular plane, distal of the tooth; BPgain – buccal plate vertical gain; PPgain – palatal plate vertical gain
[1]T – test;
[2]Mann–Whitney test, *statistically significant

The mean vertical movement of orthodontically extruded teeth was 1.52 mm, demonstrating a significant increase compared to control group (0.11 mm).

The length of extruded teeth in experimental group reduced (−1.30 mm ± 0.84 mm, p = 0.000). The distances from BP and PP tip to enamel-cement junction significantly increased in experimental group (p = 0.004). The Table 1 reveals significant increase of mesial interproximal bone septum (p = 0.008) and BP gain (p = 0.002) surrounding the teeth that were orthodontically extruded, compared to the measurements on non-treated teeth. However, there was no significant difference between changes in distal interproximal bone septum, PP gain and BP/PP thickness on both levels of measurement in experimental and control group.

Table 2 presents linear regression analysis of association of vertical tooth movement (VM) and observed parameters. In the multivariate linear regression model in which vertical tooth movement was used as dependent

Table 2. Linear regression analysis of association of vertical tooth movement and observed parameters

Parameters	Univariate model	Sig.	Multivariate model	Sig.
			[b]R^2_{adj}=0.90	
	[a]B (95% CI)		[a]B (95% CI)	
ΔL	−0.744 (−1.207 – (−0.280))	p = 0.003*	−0.205 (−0.515 – 0.105)	p = 0.181
ΔIS mesial	0.820 (0.481 – 0.910)	p = 0.000*	0.373 (0.58 – 0.574)	p = 0.019*
ΔIS distal	0.725 (0.426 – 1.044)	p = 0.000*	−0.14 (−0.329 – 0.301)	p = 0.927
BPgain	0.889 (0.851 – 1.354)	p = 0.000*	0.459 (0.202 – 0.938)	p = 0.004*
PPgain	0.701 (0.358 – 0.945)	p = 0.000*	0.177 (−0.60 – 0.390)	p = 0.142

Δ – difference between two measurements; L – length of the tooth in sagittal projection; ISmesial – height of interdental septum measured from its tip to maxillary or mandibular plane, mesial of the tooth; ISdistal – height of interdental septum measured from its tip to maxillary or mandibular plane, distal of the tooth; BPgain – buccal plate vertical gain; PPgain – palatal plate vertical gain
[a]Unstandardized coefficient B;
[b]Adjusted coefficient of determination; *Statistically significant difference

variable, the following explanatory variables were found to be independent predictor of variability among patients: ΔISmesial, BPgain, (Table 2).

In order to analyze the agreement of paired measurements conducted by the same researcher, the ICC was calculated for each variable measured. ICC was higher than 0.70 for each variable measured (the lowest ICC value was for BP/EC, 0.74 (0.35–0.91)), which was considered as good reliability. ICC values for variables L, CO/SpP, BPthick1 and ISm were higher than 0.90, which was considered as excellent reliability.

DISCUSSION

This study is among a few other studies that used CBCT scans to evaluate alveolar bone dimensional alterations, surrounding orthodontically extruded teeth [20]. OE was performed with straight-wire fixed appliances that produced light vertical forces.

When comparing the changes in BP and PP thickness between the study and control groups we found no significant differences for values measured in both levels (level 1 and 3). This finding could imply that in the study group, the use of light and continuous forces during orthodontic treatment caused tooth extrusion along its central axis, removing the pressure against the buccal cortical bone that could, according to some authors [21], generate bone fenestration.

External apical root resorption is a typical side effect of orthodontic treatment [22]. It is a decrease in root length affecting the apices caused by multiple, internal and external factors [22, 23]. The majority of resorption is clinically insignificant [24], however severe root resorption could lead to greater tooth mobility in all direction and eventually to tooth loss [22]. The difference in root length between the final and initial measurements differed significantly between the study and control group, indicating that orthodontic treatment caused external apical root resorption. However, a detailed clinical examination and CBCT scan analysis confirmed that the resorption was clinically insignificant.

In this prospective clinical study, participants from study and control group were age-matched. Time interval between initial and final measurements differ insignificantly between groups which allows us to monitor changes in bone tissue in patients with and without ongoing orthodontic treatment in the same time frame. To the best of our knowledge, this is the first prospective clinical study that observed bone changes after OE with control group of healthy participants in Serbian population.

The results given above showed that the vertical levels of BP and mesial IS could be significantly increased by OE of infraocclusal teeth. Extrusive forces provide the correction of the defects in alveolar bone by inducing the growth of periodontal tissues [25]. Vertical movement of the tooth is followed by periodontal fibers stretching [21, 26]. In order to increase the rate of tooth movement, a suitable load need to be provided [27]. As a result, a new bone is formed in the direction of the movement. The success of OE in producing new bone depends on an intact attachment periodontal fibers spanning at least one fourth of the apical region [28]. In this study, one of the inclusion criteria was that the tooth should have an intact periodontal ligament.

There is a great number of studies regarding forced eruption of the teeth with poor prognosis as a method for preserving alveolar ridge for dental implant insertion [16, 21, 28]. Papadopoulou et al. [20] stated that orthodontic forced eruption results in increase in the heights of palatal and proximal alveolar bone and significant reduction in the BP height. After performing forced eruption, a satisfactory amount of bone apposition may be detected [29].

In this study, OE was performed as much as the infraocclusal position of the tooth indicated. There were no extractions of extruded teeth. Although BP height (BPgain) increased significantly as a result of OE, PP height (PPgain) did not ($p = 0.077$). Regarding the number of participants included in this study, it can be stated that, with larger number of participants, the increase in PP height might be more significant.

Results showed that the distance from BP tip to EC increased (ΔBP/EC) in experimental group, which means that the vertical tooth movement did not convert completely into new bone. However, there was a significant vertical movement of extruded teeth, followed by apposition of surrounding buccal and mesial interproximal bone. OE was performed on 11 anterior teeth. There were six canines that were extruded, and in each case orthodontic treatment followed the extraction of four first bicuspids. Bone loss can be influenced by treatment involving extractions [30]. We expected significant increase in the height of mesial and distal IS in experimental group. The results implied that the height of mesial interproximal bone did increase significantly, but distal, next to the extraction socket, did not. Initial CBCT scans were made before the extraction of first bicuspids and the extraction itself could affect the vertical level of distal interproximal bone in treated group.

It should be kept in mind that there are difficulties in controlling the directions of the tooth movement, by using fixed orthodontic appliance in straight wire technique, in leveling stage of treatment. Besides vertical movement, there are accessory teeth movements in different directions too. Therefore, different effects of alveolar bone change in buccal, palatal or interdental region can be expected.

In our linear regression model, it was found that mesial IS height change (ΔISmesial) and BPgain could be used as independent predictors which describe 90% variabilities amongst patients regarding vertical tooth movement.

CONCLUSION

This study showed that OE affects alveolar bone levels, especially by gaining hard tissue buccal and mesial of the extruded teeth, in the same direction as the teeth moved. The thickness of PP and BP also changes, which might be a result of bone remodeling, during orthodontic treatment.

Conflict of interest: None declared.

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Ефекат ортодонтске екструзије на алвеоларну кост – проспективна клиничка студија

Иван Арсић[1], Немања Маринковић[1], Мирослав Драговић[2], Дејан Стаменковић[3], Зорана Стаменковић[1], Ненад Недељковић[1]

[1]Универзитет у Београду, Стоматолошки факултет, Клиника за ортопедију вилица, Београд, Србија;
[2]Универзитет у Београду, Стоматолошки факултет, Одељење за медицинску статистику и информатику;
[3]Универзитет у Београду, Стоматолошки факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Ортодонтска екструзија је поступак померања зуба у вертикалном, коронарном правцу. Овај покрет изазива промене у пародонталном лигаменту и доводи до стварања нове алвеоларне кости.

Циљ рада је био да се утврде промене на букалној, палатиналној и интерденталној алвеоларној кости као резултат ортодонтске екструзије.

Методе Експерименталну групу чинило је шест пацијената код којих су у оквиру ортодонтског третмана примењени фиксни апарати; контролну групу чинила су четири пацијента без примењеног ортодонтског третмана. Снимак циљане регије компјутеризованом томографијом је био направљен код свих пацијената (почетни и финални). Дужина зуба, најкраћа удаљеност од центра отпора зуба до референтне равни, растојање од врха букалне или палатиналне ламеле до споја глеђно-цементне границе, висина интерденталног септума, вертикално повећање и промена дебљине букалне и палатиналне ламеле мерени су на почетним и крајњим томографијама у обе групе.

Резултати У експерименталној групи уочена је смањена дужина екструдираног зуба. Удаљеност од врха букалне и палатиналне ламеле до глеђно-цементне границе, мезијални интерпроксимални септум кости и висина букалне ламеле значајно су повећани у експерименталној групи. Није уочена значајна разлика у дисталном интерпроксималном коштаном септуму, повећању палатиналне ламеле и дебљини букалне/палатиналне ламеле између група.

Закључак Ортодонтска екструзија утиче на ниво алвеоларне кости добијањем коштаног ткива букално и мезијално од екструдираних зуба, док се дебљина букалне и палатиналне ламеле незнатно мења.

Кључне речи: ортодонтска екструзија; ниво алвеоларне кости; компјутерска томографија с конусним снопом

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Role of HEART score in prediction of coronary artery disease and major adverse cardiac events in patients presenting with chest pain

Tanja Stojković[1], Eva Stojković[1], Dejan Sakač[2,3], Aleksandar Redžek[2,3], Anastazija Stojšić-Milosavljević[2,3], Lazar Velicki[2,3], Biljana Parapid[4,5]

[1]Novi Sad Primary Healthcare Center, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia;
[4]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[5]University Clinical Centre of Serbia, Division of Cardiology, Belgrade, Serbia

SUMMARY

Introduction Chest pain (CP) diagnostics accuracy remains debatable for both general practitioners (GP) or emergency department (ED) physicians for patients in HEART score (HS) low- and intermediate-risk groups which prompted us to review our electronic database for all patients admitted via our center's ED during 2014 to 2020 for CP and suspect acute coronary syndrome.

Methods Patients were divided in function of low- or intermediate-risk HS and assessed during a three month follow up for angiogram results, major adverse cardiac events (MACE), lab results and echo parameters.

Results Of 585 patients included, low-risk HS group (21,4%, 36% were women) had significant coronary disease on angiogram in 68%, while for intermediate-risk HS group (78.6%, with 32.6% women) it was for 18.4% of patients ($p < 0,0005$). Area under the ROC curve of HS in detecting patients with ischemic heart disease as a cause of CP was 0.771 (95% CI: 0.772–0.820) with best cut-off point HS was calculated at 3.5. Sensitivity and specificity were 89.2% and 57.6% respectively. Adjusting for sex, lab results and HS, AUROC curve of this model was 0.828 (95% CI: 0.786–0.869; $p < 0,0005$) with cut-off of 77.95. Sensitivity and specificity were 84.9% and 68% respectively. In the three-month follow-up post-discharge, there was a significant difference in MACE between groups (low- *vs*. intermediate-risk HS was 3.4 *vs*. 16.7% $p < 0.05$).

Conclusion HS for our CP patients admitted via our ED by GP and ED physicians' referral, provides a quick and reliable prediction of ischemic heart disease and MACE.

Keywords: Chest pain; HEART score; MACE; general practitioner

INTRODUCTION

Between 20% and 40% of general population experience some kind of chest pain (CP) during life [1] and the first to see the patient is the general practitioner (GP), while many of these patients are ultimately sent to the hospital for further diagnostics or intervention. In the United States, 2–5% of patients with an acute coronary syndrome (ACS) are misdiagnosed and inappropriately discharged, even from emergency department (ED) [2]. Therefore, some clinicians refer patients to additional diagnostic procedures aiming to establish the cause of CP, even in the case of a low-risk patients, leading to increased resource utilization [3, 4]. A small number of studies evaluated the accuracy of initial diagnosis in patients with CP in primary health care, especially concerning ischemic heart disease (IHD), with no data about final treatment outcomes in patients with initial misdiagnosis [5]. In the great majority of patients with CP, GPs considered coronary artery disease (CAD) unlikely diagnosis. This initial assessment agrees with the findings of various epidemiological studies in the field of primary care, which describe IHD prevalence of 8% to 15% [6, 7]. Set against this is IHD prevalence of over 50% in patients who present to a hospital ED with CP [8, 9]. The first opinion of the GP regarding presence of IHD showed at best moderate diagnostic accuracy, with a sensitivity of 68% [10]. One of the most challenging tasks GPs face is to adequately triage patients with undifferentiated CP. Often, it is not an easy task because CP evaluation is frequently subjective and different between GP, other clinicians and cardiologists. To accurately manage the cause of CP, GP or ED clinician should use some of the easily accessible and applicable tools for identification of low-risk CP patients, suitable for discharge with deferred additional diagnostics. Some of these scores are Thrombolysis in Myocardial Infarction (TIMI) score; The Platelet Glycoprotein IIb/IIIb in Unstable Angina–Receptor Suppression Using Integrilin Therapy score; Global Registry of Acute Coronary Events score; Fast Revascularization in InStability in Coronary Disease score and History, ECG, Age, Risk factors, T-troponin (HEART) score. Six, Backus and Kelder developed the HEART score (HS)

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Correspondence to:
Aleksandar REDŽEK
University of Novi Sad
Faculty of Medicine
Institute of Cardiovascular Diseases of Vojvodina
Put dr Goldmana 4
21204 Sremska Kamenica
Serbia
aleksandar.redzek@mf.uns.ac.rs

in 2008, as a rapid risk stratification tool for patients with CP to help identification of low-risk patients, suitable for earlier ED discharge [11]. While the latest AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Chest Pain recommend the TIMI score for the initial evaluation of a patient with CP [1], it is not the best tool for identification of low-risk CP patients [12, 13]. For this subset of patients, HS achieved better results, as well as in patients with a high risk of major adverse cardiac events (MACE). The negative predictive value of HS is superior compared to other scoring systems. This study aimed to estimate sensitivity and specificity of the HS in our patient population for detection of positive coronary angiography finding and its correlation with MACE in low-risk patients' subset presenting with CP.

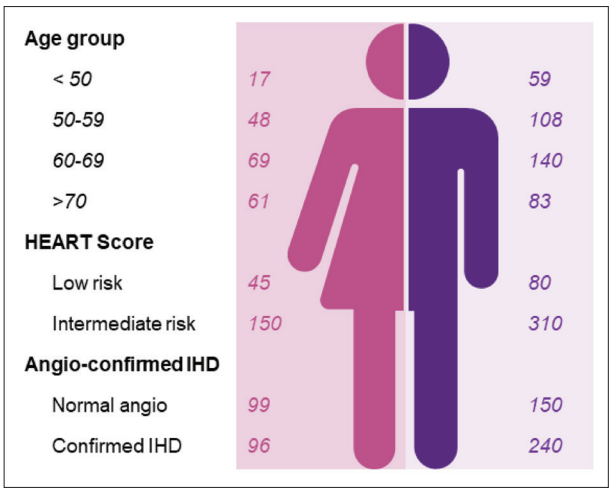

Figure 1. Sex differences in description of HEART score and angiography results
IHD – ischemic heart disease

METHODS

In this retrospective follow-up study approved by the local Ethics Committee (No 3674/10 of December 11, 2019), we analyzed patients with CP and suspected ACS who presented to Institute of Cardiovascular Diseases of Vojvodina's ED, in the period between 2014 and 2020.

Inclusion criteria were as follows: age over 21 years; CP; percutaneous coronary angiography or CT coronary angiography upon admission; biochemical analysis of high sensitivity Troponin (hsT) and calculated HS from 0 to 6. Exclusion criteria were *de novo* ECG changes (ST elevation or denivelation of more than 1 mm); hypotension and calculated HS 7 to 10.

HS is consistently validated rapid use risk stratification tool for patients with CP in the ED, considering History, ECG, Age, Risk factors and Troponin. In each category are three possible scores: 0.1 and 2. Final HS is sum of five single category scores. In this study we analyzed value of low-risk (0–3) and intermediate-risk (4–6) HS in prediction of IHD and MACE. Patients with CP were chosen randomly to achieve a minimum of 120 patients' group with a HS 0–3 (HS 0–3) and minimum of 120 patients in the group of HS ranging 4–6 (HS 4–6). All of these patients were admitted to the hospital and underwent coronary angiography. Degree of coronary artery stenosis greater than 50 % was defined as significant. The follow-up period for both groups of patients was three months post-discharge during which we assessed difference between groups' survival and incidence of MACE defined as new ACS, stroke, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and IHD-related death. In addition to validation of HS in prediction of IHD and MACE, we analyzed predictive value of creatine kinase MB and fasting glucose levels; ejection fraction and left ventricle volumes and diameters. The data were provided from hospital database and by calling patients and their families in case of their further medical treatment in other hospital. Statistical analysis included descriptive statistics such as arithmetic mean, standard deviation, median, quartile, frequency and percentages. Comparison of mean values of variables of two groups of patients was realized by t – test and Mann–Whitney test. Categorical variables were compared with the χ^2 test or Fisher exact test. Univariate and multivariate binary logistic regression we used to determine influence of variables on final outcomes. Predictive values of variables were estimated with the ROC curve. Two-sided P values of less than .05 were considered to be significant for all analyses. All statistical analyses were performed with SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 585 patients with CP enrolled in the FU study, 125 patients (21.4%) were in low-risk HS group (HS 0–3) and 460 patients (78.6%) in the intermediate-risk HS group (HS 4–6). Sex distribution was similar for both groups (36% in HS 0–3 *vs.* 33.6% in HS 4–6) and together with sex-specific description for HS and angiography are presented in Figure 1. Number of patients with hypertension was significantly higher in HS group 4–6 (HS 4–6 74% *vs.* HS 0–3 63%; $p < 0.05$). Previous myocardial infarction (MI), PCI and CABG were predominant in intermediate-risk HS group (previous MI/PCI/CABG HS 4–6 15.7/15.7/5.4 % *vs.* HS 0–3 1.6/2.4/0 %; $p < 0.05$). The distribution of other risk factors in the two groups is shown in Table 1. Echocardiography data analysis showed a significant difference between groups in left ventricular ejection fraction, diameters and volumes – both systolic and diastolic (Table 2.). Lab results of interest showed significantly higher blood levels of creatine kinase MB, urea and creatinine in intermediate-risk HS group (Table 3.). Invasive coronary imaging was performed in higher percentage in intermediate-risk HS group (HS 4–6 83.7% *vs.* HS 0–3 64.8%; $p < 0.0005$), while others were offered non-invasive, CT coronary angiography. There was significant difference in coronary angiography findings between groups. In intermediate-risk HS group, significant coronary disease (stenosis > 50%) was present in 68% of patients *vs.* low-risk HS group where IHD was confirmed in 18.4% of patients ($p < 0.0005$). Patients with

Table 1. Distribution of different variables in HEART score groups

Variables	HS 0–3	HS 4–6	p
Sex Men Women	 80 (64%) 45 (36%)	 310 (67.4%) 150 (32.6%)	0.544
Hypertension	79 (63.2%)	341 (74.1%)	0.022
Smoking	43 (34.4%)	167 (36.3%)	0.773
Hyperlipoproteinemia	37 (29.6%)	170 (37%)	0.156
Diabetes mellitus	23 (18.4%)	74 (16.1%)	0.631
Previous myocardial infarction	2 (1.6%)	72 (15.7%)	< 0.0005
Previous PCI	3 (2.4%)	72 (15.7%)	< 0.0005
Previous CABG	0	25 (5.4%)	0.004
Previous stroke	2 (1.6%)	14 (3%)	0.542
Troponin	11 (8.8%)	188 (40.8%)	< 0.0005
Mitral valve insufficiency	6 (5%)	47 (10.8%)	p = 0.012
Aortic valve insufficiency	8 (6.6 %)	25 (5.7%)	p = 0.745

HS – HEART score; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting

Table 2. Echocardiographic data analysis in HEART score groups

Variables	HS groups	Percentiles			p
		25th	50 (median)	75th	
EF	HS 0–3	55	60	61	< 0.0005
	HS 4–6	47	55	60	
IVSd	HS 0–3	1.10	1.20	1.30	0.113
	HS 4–6	1.10	1.20	1.30	
PLWd	HS 0–3	1.05	1.20	1.30	0.192
	HS 4–6	1.10	1.20	1.30	
LVIDs	HS 0–3	2.65	3	3.40	0.005
	HS 4–6	2.80	3.20	3.70	
LVIDd	HS 0–3	4.50	4.75	5.10	0.001
	HS 4–6	4.60	4.90	5.30	
EDVLV	HS 0–3	72.50	91	115	0.002
	HS 4–6	80	100	121	
ESVLV	HS 0–3	29.50	38.50	52	< 0.0005
	HS 4–6	34	46	61	

HS – HEART score; EF – ejection fraction; IVSd – interventricular septal diameter; PLWd – posterior wall thickness at end-diastole; LVIDs – left ventricular internal dimension at end-systole; LVIDd – left ventricular internal dimension at end-diastole; EDVLV – end-diastolic volume of the left ventricle; ESVLV – end-systolic volume of left ventricle

Table 3. Biochemical data analysis in HEART score groups

Variables	HS groups	Percentiles			p
		25th	50 (median)	75th	
CK-MB	HS 0–3	16	20	27.50	0.012
	HS 4–6	18	25	40	
FG	HS 0–3	5.45	6.15	7.25	0.524
	HS 4–6	5.70	6.40	8	
s-Urea	HS 0–3	4.30	5.40	7.40	0.041
	HS 4–6	5.10	6.30	8.60	
s-Creatinine	HS 0–3	74	86	98	< 0.0005
	HS 4–6	81	98	114.50	
CRP	HS 0–3	2.30	4.20	10	0.224
	HS 4–6	2.85	5.70	13.50	
LDH	HS 0–3	165	194	236	0.220
	HS 4–6	170.50	200	245.50	

CK-MB – creatine kinase MB; FG – plasma fibrinogen; CRP – C-reactive protein; LDH – lactate dehydrogenase

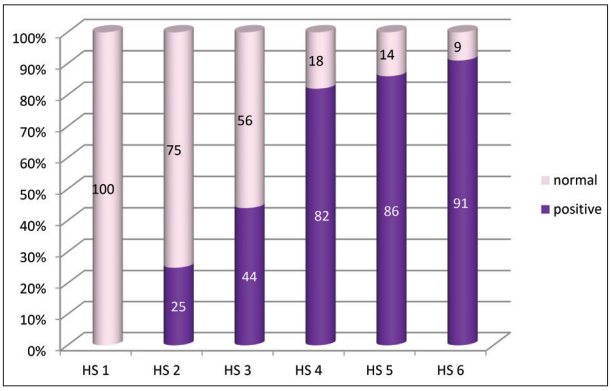

Figure 2. Influence of HEART score value on positive coronary angiography finding

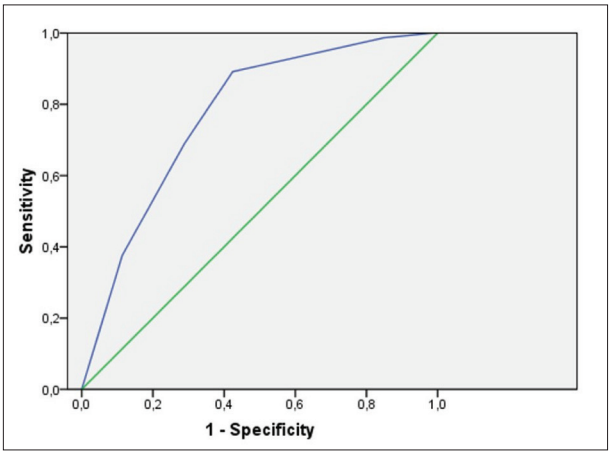

Figure 3. ROC curve of HEART score in detecting patients with ischemic heart disease

confirmed IHD on coronary angiography, had two- and three-vessel CAD. There was no difference between HS groups in distribution of patients according to severity of the CAD. In both HS groups, approximately two thirds of IHD-confirmed patients had significant stenosis of two and more vessels (HS 0–3 65.2% *vs.* HS 4–6 70%; p = 0.642). Patients with HS 1 were free of CAD. Results for other HS subgroups are shown in Figure 2. The area under the ROC curve of HS in detecting patients with IHD as a cause of CP was 0.771 (95% CI:0.772–0.820). The best cut-off point for the HS in this regard was calculated at 3.5. The sensitivity and specificity were 89.2% and 57.6% respectively (Figure 3.).

Binary logistic regression was used to show influence of different factors of confirmed CAD. The odds ratio (OR) for HS groups was 11.653 (7.094–19.143). Intermediate-risk HS group had 11.6-time higher risk of having IHD compared to low-risk HS group. Creatine kinase MB and glucose blood level odds ratios were 1.022 (1.006–1.038) and 1.131 (1.019–1.256) respectively. Results are shown in Table 4.

Integrating sex, creatine kinase MB, glucose blood level and HS, the AUROC curve of this model was 0.828 (95% CI:0.786–0.869; p < 0.0005). The cut-off point was 77.95. The sensitivity and specificity were 84.9% and 68% respectively (Figure 4.).

Table 4. Results of univariate and multivariate binary logistic regression for different variables

Variable	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Sex	0.60 (0.403–0.895)	0.012	0.587 (0.357–0.966)	0.036
History	1.376 (1.079–1.754)	0.010	/	ns
ECG	2.615 (1.819–3.761)	< 0.0005	/	ns
Troponin	3.607 (2.371–5.486)	< 0.0005	/	ns
EF	0.952 (0.929–0.976)	< 0.0005	/	ns
LVIDd	1.414 (1.052–1.899)	0.021	/	ns
LVIDs	1.449 (1.029–2.041)	0.034	/	ns
EDVLV	1.010 (1.003–1.016)	0.003	/	ns
ESVLV	1.015 (1.005–1.024)	0.002	/	ns
CK-MB	1.026 (1.012–1.040)	< 0.0005	1.022 (1.006–1.038)	0.006
FG	1.137 (1.031–1.254)	0.010	1.131 (1.019–1.256)	0.021
HEART score	11.190 (7.099–17.637)	< 0.0005	11.653 (7.094–19.143)	< 0.0005

ECG – electrocardiogram; EF – ejection fraction; LVIDd – left ventricular internal dimension at end-diastole; LVIDs – left ventricular internal dimension at end-systole; EDVLV – end-diastolic volume of the left ventricle; ESVLV – end-systolic volume of left ventricle; CK-MB – creatine kinase MB; FG – plasma fibrinogen

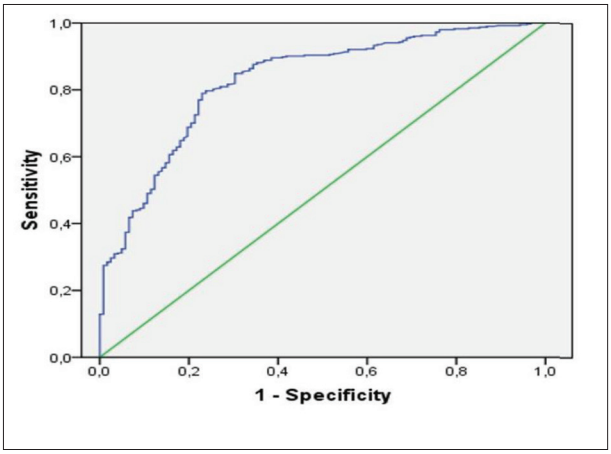

Figure 4. ROC curve of integrated sex, creatine kinase MB, glucose blood level and HEART score in detecting patients with ischemic heart disease

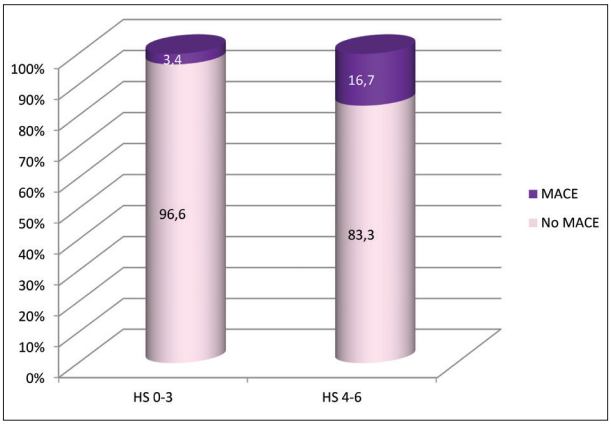

Figure 5. Incidence of MACE in HEART score groups

In three-months follow-up period post-discharge, there was significant difference in MACE between groups (HS 0–3 3.4% *vs*. HS 4–6 16.7% p < 0.05) (Figure 5.).

DISCUSSION

HS is a risk stratification score used for patients with CP with suspected non-ST elevation ACS. Simple to use and widely validated as a risk stratification tool, its accuracy is still somewhat questioned for predictive power in detecting of significant CAD.

Our study included patients who were admitted to the cardiology department as a result of a physician's clinical decision. The present study showed 21.4% of patients, with CP who met inclusion criteria, classified as low-risk HS patients. This result is not consistent with the study by van Meerten et al. [14] where low-risk HSs were calculated in 36.4% of the patients, while Soares et al. reported low-risk HS present in 33% of patients by research generated score and 25% by ED clinician score [15]. In a meta-analysis of 25 studies published from 2010 to 2017, with a total of 25,266 patients, 39.3% were deemed to have low-risk HS [16]. A lower percentage of low-risk HS patients in our study should be explained by the study population selected only from patients admitted according to inclusion criteria.

Hypertension, ACS with/without previous PCI and CABG, as a part of HEART scoring criteria, were present in expectedly higher percentage in the intermediate-risk HS group. There was a significant difference between groups in ejection fraction; systolic and diastolic diameters and volume of left ventricle with lower ejection fraction and larger diameters and volumes of the left ventricle in intermediate-risk HS group as a result of impaired left ventricular function caused by IHD which is present in higher percentage in this group of patients – all to be expected with a pre-existing burden of disease.

In our study, we determined the HS to be a diagnostic predictor of severe coronary artery stenosis (minimum one coronary artery stenosis >50%) with positive findings in 18.4% of patients in low-risk group and 68% of patients in the intermediate-risk group. The area under the ROC curve of HS in detecting patients with IHD as a cause of CP was 0.771 (95% CI: 0.772–0.820). The best cut-off point for the score in this regard was calculated in 3.5. The sensitivity and specificity were 89.2% and 57.6% respectively. In a paper published by Han et al. [17], where significant coronary artery stenosis was defined more than 70%, they found that the diagnostic accuracy of the HS is better for significant coronary artery stenosis than for ACS. They demonstrated that HS can be considered a useful tool for determining early invasive measures based on the objective results of coronary visualization. Backus et al. [18] lowered the value of the risk factor element and weighted history and troponin elements. There was some improvement in calibration and discrimination, but its clinical usefulness was relatively small. We had a different approach in modifying the HS by integrating sex, creatine kinase MB, glucose blood level and HS. Compared with the sensitivity

and specificity of the HS, our modification had nearly the same sensitivity, but improved specificity.

The three-months follow-up post-discharge, showed a significant difference in MACE between groups (low-HS 3.4% *vs*. intermediate-HS 4–6 16.7% $p < 0.05$). Reported incidence of MACE in the low-risk HS group by van Meerten et al. [14] was in 1.7% of patients which should be basis to skip redundant testing and move to quicker discharge. Oh and coworkers found a 0.6% risk of MACE in low-risk CP patients from North Carolina [19]. The higher incidence of MACE in our study population should be explained by the possible presence of other risk factors that are not included in the HS.

Implementation of HS in the routine practice of GP or ED physicians, should avoid further unnecessary observation and noninvasive and invasive cardiac testing. Admission of low-risk patients for further examination is time-consuming, expensive, and in some cases harmful. A widespread invasive cardiac testing may lead to patient harm. One example is radiation exposure [20] since a dose of 10 mSv may increase the risk of fatal cancer, which can be a public health concern in the reality of the increased number of diagnostic tests including radiation exposure [21]. Also, introduction of HEART scoring cut costs over $4.5 million annually and invasive imaging in a similar sized sample as ours [4].

There is evidence that HS compares favorably with other CP decision scores. TIMI score, when applied to patients with undifferentiated CP has not performed as well, with a poor prognostic ability [22].

Although a detailed sex-specific analysis was not the scope of this publication, our low-risk HS and intermediate-risk HS groups encompassed 36% *vs*. 32.6% women respectively, in a representative sample for the region where awareness of heart disease in women is very physician-dependent [23]. Also, additional imaging needed for patients who were considered lacking angiographically significant stenoses, was not routinely provided in the investigated period irrelevant of sex, although long-term clinical benefits are well known, especially for women [24, 25, 26].

Preciado et al. [27], in a far larger sample size, but time-frame-wise appropriate with ours, noted women were hospitalized or received stress testing less frequently than men for low-HS (18.8% *vs*. 22.8%; OR 0.79; 95% CI 0.73–0.84) and intermediate-HS (46.7% *vs*. 49.7%; OR 0.88; 95% CI 0.83 to 0.95), although their outcomes were better, finding it still inappropriate. Still, per latest data women and patients of color remain those less likely to receive HS risk stratification when presenting with undifferentiated CP [28]. However, although – per latest United Nations High Commissioner for Refugees and UNICEF reports – since 2015, more than 1.5 million refugees and migrants have passed through Serbia, while during 2020, the number of refugees and migrants present in Serbia at any given time was around 7,000 and accommodated in reception, transit and asylum centers around 6,000 [29] which is the upper cut off for country's hosting limit [30], our reported sample was native Caucasian population not out of discrimination, but management system of refugee populations is handled differently.

Study limitations

Limitations of our study include single-center, retrospective design and a small sample size with limited projection to the whole population that is mainly Caucasian White. The HS was not applied to all CP patients, but rather those with met inclusion criteria including percutaneous coronary angiography or CT coronary angiography upon admission to our tertiary level University hospital.

CONCLUSION

Use of HS scoring system for patients with CP who presented to our center's ED by GP referral of our own ED physicians' one provided a quick and reliable prediction of IHD as a cause of CP and MACE. Appropriate assessment of borderline patients with traditionally called "atypical" we nowadays term "sex specific" symptoms, should be improved by application of HS in routine practice by both GP and ED physicians aiming to stratify better populations deemed of intermediate or low-risk, in particular women whose awareness for CAD needs to be improved.

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HEART скор у предикцији коронарне болести и значајних нежељених кардиоваскуларних догађаја код болесника са болом у грудима

Тања Стојковић[1], Ева Стојковић[1], Дејан Сакач[2,3], Александар Рељек[2,3], Анастазија Стојшић-Милосављевић[2,3], Лазар Велицки[2,3], Биљана Парапид[4,5]

[1]Дом здравља Нови Сад, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Институт за кардиоваскуларне болести Војводине, Сремска Каменица, Србија;
[4]Универзитет у Београду, Медицински факултет, Београд, Србија;
[5]Универзитетски клинички центар Србије, Клиника за кардиологију, Београд, Србија

САЖЕТАК

Увод Прецизност дијагностике бола у грудима остаје најдискутабилнија за лекаре како опште праксе, тако и ургентних центара за болеснике ниског и средњег *HEART* скора (ХС), што нас је навело на ретроспективну анализу наших електронских историја болести у циљу процене свих хоспитализованих због бола у грудима са сумњом на акутни коронарни синдром преко нашег Ургентног центра у периоду 2014–2020.

Методе Болесници су подељени у групе ниског и средњег ХС и у тромесечном праћењу процењивани су резултати коронарографије, великих кардиолошких нежељених догађаја (*MACE*), лабораторијски резултати и ехокардиографски параметри.

Резултати Од 585 укључених болесника, у групи ХС ниског ризика (21,4%, 36% жена) ангиографски значајну коронарну болест је имало 68%, док у групи ХС средњег ризика (78,6%, 32,6% жена) то је случај са 18,4% болесника ($p < 0,0005$). Регија под *ROC* кривом ХС за детекцију болесника са коронарном болешћу као узроком бола у грудима била је 0,771 (95% *CI*: 0,772–0,820) са *cut off*-ом ХС 3,5. Сензитивност и специфичност су биле 89,2%, тј. 57,6%. Интеграцијом пола, лабораторијских параметара и ХС, *AUROC* крива за овај модел је била 0,828 (95% *CI*: 0,786–0,869; $p < 0,0005$) са *cut off*-ом од 77,95. Сензитивност и специфичност су биле 84,9%, тј. 68%. Током тромесечног праћења по отпусту, забележена је значајна разлика у *MACE* између две групе (ХС ниског спрам средњег ризика била је 3,4 према 16,7% $p < 0,05$).

Закључак ХС за наше болеснике са болом у грудима примљене кроз наш Ургентни центар по упуту како лекара опште праксе, тако и лекара Ургентног центра, представља брз и поуздан предиктивни скор за коронарну болест и *MACE*.

Кључне речи: бол у грудима; *HEART* скор; *MACE*; лекар опште праксе

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The *VKORC1* and *CYP2C9* gene variants as pharmacogenetic factors in acenocoumarol therapy in Serbian patients – consideration of hypersensitivity and resistance

Ljiljana Rakićević[1], Mirjana Kovač[2,3], Dragica Radojković[1], Milica Radojković[2,4]

[1]University of Belgrade, Institute of Molecular Genetics and Genetic Engineering, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Blood Transfusion Institute of Serbia, Hemostasis department, Belgrade, Serbia;
[4]Dr Dragiša Mišović – Dedinje University Clinical Hospital Center Clinic of Internal Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Coumarin therapy represents one of the best models for applying pharmacogenetics. The contribution of factors influencing coumarin therapy can vary significantly between ethnic groups, which justifies conducting population-specific studies. The aim of this study was to analyze the influence of the most important genetic factors (*VKORC1* and *CYP2C9* genes) that affect coumarin therapy in patients from Serbia.

Methods A retrospective study involving 207 patients on acenocoumarol therapy was conducted. Genetic analyses were performed by direct sequencing. Influence on acenocoumarol dose of variants (*VKORC1*, *CYP2C9*2, CYP2C9*3*) causing hypersensitivity and *VKORC1* variants causing resistance to acenocoumarol were analyzed. Multiple regression analysis was used to design a mathematical model for predicting individual drug dosage based on clinical-demographic and genetic data.

Results The study confirmed significant influence of the analyzed genetic factors on acenocoumarol maintenance dose. We designed mathematical model for predicting individual acenocoumarol dose and its unadjusted R2 was 61.8. In the testing cohort, our model gave R2 value of 42.6 and showed better prediction in comparison with model given by other authors. In the analyzed patients, nine different variants in the *VKORC1* coding region were found. Among carriers of these variants 78% were completely resistant, and it was not possible to achieve therapeutic effect even with high doses of acenocoumarol.

Conclusions Population-specific model for prediction individual dose of acenocoumarol, may show advantages over protocols that are used in a generalized manner. Also, *VKORC1* variants which cause coumarin resistance should be considered when planning therapy.

Keywords: pharmacogenetics; coumarin derivatives; acenocoumarol; *VKORC1*; *CYP2C9*

INTRODUCTION

Coumarin derivatives or coumarins (warfarin, acenocoumarol, phenprocumon) are oral anticoagulants which act by inhibiting the synthesis of vitamin K-dependent clotting factors and they are widely prescribed for treatment and prevention of thrombosis [1]. Although coumarin derivatives are very effective on average, their use represents a great challenge in some patients and it is particularly notable during therapy initiation. It is a matter of narrow therapeutic window and inter-individual differences in drug dosage needed for achieving therapeutic effect (given as International Normalized Ratio – INR), as well as intra-individual differences in the required dose over time. As a result, patients require frequent control, but even with careful monitoring and titration towards a patient's maintenance dose, coumarin therapy is often subtherapeutic, or supratherapeutic [2, 3].

Pharmaceutical industry managed to launch new anticoagulant drugs, as alternative to coumarin derivatives, in the form of direct inhibitors of certain coagulation factors (thrombin or FX-a). Direct oral anticoagulants offer much more comfortable use due to therapeutic effects without large inter-individual fluctuations and due to no need to check INR values [4]. However, despite their benefits, new anticoagulants are not the right choice for all patients (e.g., patients with artificial valves) [5].

Significant possibilities for understanding and overcoming problems related to use of coumarin derivatives, have been presented by personalized medicine. It is previously established that patient's response to coumarins depends on several acquired factors such as age, dietary intake, intercurrent illness and other drugs [6, 7, 8]. Pharmacogenetic research has made the biggest contribution to understanding inter-individual differences related to therapeutic effects of coumarin. They have demonstrated that certain variants of gene influencing pharmacodynamic (*VKORC1*) and pharmacokinetic (*CYP2C9*) of coumarins have the biggest impact on therapeutic effects of these drugs.

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Correspondence to:
Ljiljana RAKIĆEVIĆ
University of Belgrade
Institute of molecular genetics and genetic engineering
Vojvode Stepe 444a
11042 Belgrade
Serbia
ljiljanarakicevic011@gmail.com

The *VKORC1* (Vitamin K epOxide Reductase Complex subunit 1) gene encodes subunit 1 of vitamin K epoxide reductase – the key enzyme of the vitamin K cycle and the pharmacological target of coumarins. A single nucleotide substitution *VKORC1*2* (c.-1639G>A; rs9923231) in the promoter region of the *VKORC1* gene results in a suppression of gene expression which leads to decreased production of the coumarin target. The *CYP2C9* gene expresses the enzyme cytochrome P450 2C9 that takes part in the hepatic metabolism of coumarins. Two variant alleles of this gene – *CYP2C9*2* (c.430C> T; rs1799853) and *CYP2C9*3* (c.1075A>C; rs1057910) – are associated with reduced enzyme activity, resulting in deficient clearance of coumarin derivatives [8, 9, 10]. It has been shown that the *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants are major genetic predictors of hypersensitivity to coumarins in Caucasians. Carriers of these allele variants need significantly lower dose, in comparison to patients who do not have these variants [8, 9]. Additionally, the variants in the coding region of the *VKORC1* gene are the main cause of coumarin resistance [9]. Several research groups worldwide presented the mathematical models for predicting individual dosage of coumarins. These models usually include clinical and demographic data as well as genetic factors associated with coumarin sensitivity, while genetic factors that cause resistance are usually omitted from these models [10, 11]. Further, it has been shown that the contribution of genetic and non-genetic factors affecting coumarin therapy may vary markedly between patients from different ethnic groups [12], which justifies conducting population-specific studies.

In this study, we set the goal to analyze the influence of major genetic factors influencing coumarin therapy, in patients from Serbia. Further, assuming that population-specific protocols may take advantage over protocols used in a generalized manner, we aimed to design a mathematical model for predicting individual drug dosage in the Serbian population based on clinical-demographic and genetic data (*VKORC1*2*, *CYP2C9*2*, *CYP2C9*3).* We also aimed to consider the possible reasons for improving pharmacogenetic strategies in coumarin administration by taking into account genetic factors that cause resistance.

METHODS

Patients

The study included patients registered in Anticoagulation Service for outpatient's treatment (the Blood Transfusion Institute of Serbia, Hemostasis Department) who were using acenocoumarol as anticoagulation therapy. Therapeutic INR value was 2–3**.** Indications for anticoagulation therapy were deep venous thrombosis, pulmonary embolism and arrhythmia. Additional criteria for including patients into the study were that they had to be the age of 18 and above. Excluded patients were those with liver or kidney dysfunction, malignant disease, as well as pregnant women and nursing mothers.

Laboratory testing and data collecting

Commercially available tests were used for standard laboratory testing. Sequencing of *VKORC1* coding region and determination of *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants were performed as previously described [13, 14]. Demographic, clinical and genetic data relevant to the study were taken from medical records existing for each patient. After data collection we did retrospective analysis of all the data for the patients included in the study. The research was conducted with the approval of the Ethical Committee of the Blood Transfusion Institute of Serbia and written consent of all the patients involved in the research.

Outcome and determinants

Mean stable acenocoumarol maintenance dose in mg/week, at the first stable period after initiation of anticoagulation therapy was used as the outcome measure. Stable maintenance dose was calculated from weekly doses that were unchanged over a minimum of three consecutive measurements of therapeutic INR. To develop prediction model, age (in years), height (in centimeters), weight (in kilograms), sex, use of amiodarone and genetic variants (*VKORC1*2*, *CYP2C9*2* and *CYP2C9*3*) are considered as determinants.

Statistical analysis

Demographic, clinical and genetic characteristics of the whole group of patients analyzed in this study are presented by descriptive statistics. Categorical variables are presented as numbers or percentages and continuous data are summarized as means and standard deviations. The normality of continuous variables was evaluated using the Kolmogorov–Smirnoff test. Allele frequencies were estimated by gene counting and departure from Hardy–Weinberg equilibrium (HW) was tested using the χ^2 test. Conjugated influence of genetic and non-genetic factors was investigated by multiple regression analysis. With the purpose of designing and testing mathematical equation i.e., model which would derive from multiple regression analysis, the patients with stable acenocoumarol maintenance dose (N = 200) were divided into two cohort – derivation cohort (N = 100) and testing cohort (N = 100) – on random basis. The differences between cohorts were tested using the χ^2 test for categorical variables and the Unpaired T test and Mann–Whitney U test for continuous variables. On the derivation cohort multiple regression analysis was applied in order to select predictors to be used for estimating the individual dose of acenocoumarol and to derive model for acenocoumarol dose prediction. The testing cohort was used for assessing the quality of the mathematical equation derived from multiple regression analysis. Also, we searched the literature for models which use similar parameters for acenocoumarol dosage prediction. These selected models proposed by other authors, were compared with model provided by our study. The coefficient of determination (R2) and the mean absolute

error (i.e., 95% confidence interval which this value takes) in the validation data set were our pre-fixed values for evaluating the designed model. For all statistical tests $p < 0.05$ was considered statistically significant.

RESULTS

General characteristics of patients

Overall, 207 patients were enrolled in the retrospective study and baseline characteristics of patients are shown in Table 1. The majority of subjects (N = 200) were patients on stabile anticoagulation therapy, i.e., in a therapeutic INR (2–3) for three months. The average maintenance dose for these patients was 18.8 mg/week. Based on the dose level, patients were divided into three groups: Low maintenance dose (< 7 mg/week), Medium maintenance dose (7–28 mg/week), High maintenance dose (> 28 mg/week). In minority of the anticoagulated patients (N = 7), it was not possible to reach therapeutic INR values, even with high doses of acenocoumarol (complete resistance). In these patients, antithrombotic therapy was continued without vitamin K antagonist by introducing direct anticoagulants.

Table 1. Demographic, clinical and genetic characteristics of analyzed patients

Characteristics (variable)	Entire group (N = 207)
Patients with achieved therapeutic INR range, N (%) Low maintenance dose, N (%) Medium maintenance dose, N (%) High maintenance dose, N (%)	200 (196.6) 43 (20.8) 127 (61.3) 30 (14.5)
Patients out of therapeutic INR range (complete resistance), N (%)	7 (3.4)
Sex (female/male)	82/125
Age (years); mean ± SD	60.46 ± 13.556
Dose (mg/week); mean ± SD	18.8 ± 11.045
Weight (kg); mean ± SD	85.09 ± 11.88
Height (cm); mean ± SD	174 ± 7.379
Amiodaron users; N (%)	15 (7.5)
Genotype; N (%)	
CYP2C9	
CYP2C9*1*1	143 (69)
CYP2C9*2*1	34 (16)
CYP2C9*2*2	3 (2)
CYP2C9*2*3	4 (2)
CYP2C9*3*1	23 (11)
HW-X2 test p-value	0.64
VKORC1	
VKORC1 *1*1	69 (33)
VKORC1 *1*2	89 (43)
VKORC1 *2*2	49 (24)
HW-X2 test p-value	0.06

INR – international normalized ratio; SD – standard deviation; N – number of patients; HW – Hardy–Weinberg equilibrium

Analysis of the *VKORC1* and *CYP2C9* variants related to sensitivity to acenocoumarol

In the group of 207 analyzed patients, 89 patients (43%) were heterozygotes and 49 patients (24%) who were homozygotes for the *VKORC1*2* variant. Also, there were 34 patients (16.4%) with C*2*1 genotype, three patients (1.45%) with C*2*2 genotype, four patients (1.93%) with C*2*3 genotype and 23 patients (11.1%) with C*3*1 genotype (Table 1). Based on these data, the frequencies of *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* alleles are 0.45, 0.11 and 0.065 respectively. Studied variant alleles were in HW equilibrium.

In the group of 207 subjects, 158 patients were carriers of at least one studied variant. In patients (N = 200) who were on stabile anticoagulation therapy, 157 patients had at least one variant associated with sensitivity to coumarins. The average maintenance dose of acenocoumarol for these patients was 16.29 mg/week and it significantly differed ($P < 0.000$) comparing to the average maintenance dose of 27.95 mg/week for patients who were *wild type* for all three analyzed variants.

Creating and testing of prediction model

To create a prediction model, which reflects complex and conjugated influence of genetic, demographic and clinical factors, we used the group of patients on stabile anticoagulation therapy (N = 200). The group was divided into two cohorts - the derivation cohort for creating prediction model and the testing cohort for its testing. 100 patients were randomly selected for each cohort. There were no statistically significant differences between the cohorts in terms of demographic and clinical characteristics, as well in terms of distribution of the studied alleles. HW equilibrium was satisfied in both general group of patients and individual cohorts (Table 2).

The logarithm of the maintenance dose value was used as a dependent variable. Multiple regression analysis was conducted on the derivation cohort. In addition to *VKORC1* and *CYP2C9* variants, age, weight and sex were identified as significant predictors of acenocoumarol dose, and unadjusted R2 was 61.8. Mathematical equation for prediction of acenocoumarol maintenance dose was designed based on the output of linear regression: dose (mg/week) = $10^{(1.39 + 0.065\ (\text{for female}) - 0.006\times\text{age} + 0.004\times\text{weight} - 0.192\ (\text{for C*1*2}) - 0.298\ (\text{for C*2*2}) - 0.269(\text{for C*2*3}) - 0.188\ (\text{for C*1*3}) - 0.11\ (\text{for V*1*2}) - 0.288\ (\text{for V*2*2}))}$.

The equation was tested on the independent group of patients - testing cohort, and compared with mathematical models for prediction of acenocoumarol dose given by highly cited model for Dutch population, given by van Schie et al. [10], and model for Greek population, given by Markatos et al. [15]. In the case of the equation given by Van She et al. [10], we also applied the mathematical conversion, given by the authors, which is needed to compare their formula with other models. Our model gave R2 value 42.6, and showed better prediction in comparison with model given by van Schie et al. [10] which value of R2 was 37.8. Also, there was a slight advantage to our model

Table 2. Demographic, clinical and genetic characteristics of patients in the derivation and the testing cohort

Characteristics (variable)	Derivation cohort (N = 100)	Testing cohort (N = 100)	P-value (derivation cohort vs. testing cohort)
Gender (female/male)	39/61	40/60	0.885*
Age (years) mean ± SD	61.64 ± 12. 498	59.27 ± 14.504	0.317 **
Dose (mg/week) mean ± SD	18.86 ± 9.68	18.74 ± 12.306	0.402 **
Weight (kg) mean ± SD	84.32 ± 12.49	85.86 ± 11	0.361 ***
Height (cm) mean ± SD	173.87 ± 7.209	174.33 ± 7.574	0.707 **
Amiodaron users N (%)	6 (6)	9 (9)	0.421 *
Genetic characteristics			
CYP2C9 genotypes N (%)			
*CYP2C9*1*1	70 (70)	66 (66)	0.544
*CYP2C9*2*1	16 (16)	18 (18)	0.706
*CYP2C9*2*2	1 (1)	2 (2)	0.561
*CYP2C9*2*3	3 (3)	1 (1)	0.312
CYP2C9 *3*1	10 (10)	13 (13)	0.506
HW-X2 test p-value	0.460	0.724	/
VKORC1 genotypes N (%)			
VKORC1 *1*1	31 (31)	32 (32)	0.879
VKORC1 *1*2	46 (46)	42 (42)	0.569
VKORC1 *2*2	23 (23)	26 (26)	0.622
HW-X2 test p-value	0.4585	0.116	/

*χ^2 test; **Mann–Whitney U test; ***Unpaired T test; SD – standard deviation; N – number of patients; HW – Hardy–Weinberg equilibrium

Table 3. Comparison of algorithms for acenocoumarol dose prediction

Algorithm	Mean weekly dose CI 95% SD	Mean absolute error CI 95%	Unadjusted R2 of authors original algorithm (%)	R2 in our testing cohort (%)
Van Sche et al. [10]	18.17 17.09–19.28 5.72	7.18 5.95–8.58	53	37.8
Markatos et al. [15]	17.77 16.52–19.22 7.01	6.77 5.53–8.14	55	41.1
Our algorithm	17.90 16.50–19.38 7.13	6.83 5.66–8.15	61.8	42.6
Real mean dose	18.74 16.40–21.26 12.31			

CI – concordance interval; SD – standard deviation

over model given by Markatos et al. [15] which R2 in our testing cohort value was 41.1 (Table 3).

Analysis of the *VKORC1* variants related to resistance to acenocoumarol

The sequencing of *VKORC1* exons was performed in order to analyze the frequency and distribution of variants causing resistance to acenocoumarol. In the analyzed group of 207 patients, nine patients with different variants of the *VKORC1* coding region were found. Detected variants and resulting amino acid substitutes with their positions in the protein are given in Table 4. Seven of nine variants detected in the *VKORC1* coding region were found in patients who had complete resistance to acenocoumarol. Two variants have been detected in patients with high maintenance (N = 30) doses of acenocoumarol. No variants in the coding region of the *VKORC1* gene were detected in patients with medium (N = 127) and low doses (N = 43).

DISSCUSION

Coumarin derivatives are still the pivot of anticoagulant therapy in Serbia. However, pharmacogenetic studies considering *VKORC1* and *CYP2C9* gene, has been focused only to therapy of smaller group of elderly patients [13]. Until now, there have not been studies examining pharmacogenetic factors in more complex manner, which would enable predicting response to anticoagulant therapy and formulating the model for using anticoagulant therapy in our population. With regard to the impact on therapeutic regiment of acenocoumarol, this study investigates two most important pharmacogenetic factors – *VKORC1* and *CYP2C9*. *VKORC1* gene dominates with its pharmacogenetic potential exhibiting variants

Table 4. Nucleotide substitution in coding region of *VKORC1* gene detected in analyzed patients

Nucleotide substitution	Amino acid substitution	Location of amino acid substitution	Effect on acenocoumarol therapy	Variants associated with sensitivity
c.76G > C	Ala26Pro	Entirely conserved place in vertebrates; the interface between the first TM helix and the ER luminal domain	Complete resistance*	Not detected
c.84C > T	His28Gln	Coumarin binding interface	Moderate resistance	Not detected
c.106G > T	Asp36Tyr	The outer surface loop	Moderate resistance	Carrier of the *CYP2C9*2*
c.160G > C	Val54leu	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.175T > C	Trp59Arg	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.176G > T	Trp59leu	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.177G > T	Trp59Cys	The large loop situated in the ER lumen between the first two TM helices; important for catalytic activity of VKORC1	Complete resistance*	Not detected
c.383T > G	Leu128Arg	The first TM helix; entirely conserved place in vertebrates	Complete resistance*	Not detected
c.368T > A	Ile123Asn	The end of TM3, adjacent to the third putative coumarins binding interface	Complete resistance*	Not detected

TM helix – transmembrane helix; ER – endoplasmic reticulum; * therapy aborted

responsible for hypersensitivity and resistance to the drugs.

As expected, the study confirmed significant influence of examined genetic factors on maintenance dose of acenocoumarol. The frequency of the *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants in analyzed sample of Serbian population has been shown as high. Over 60% of patients in the entire group were carriers of the *VKORC1*2* variant allele. Additionally, almost 80% of patients had at least one of the studied variant alleles and the average weekly dosage of acenocoumarol in these patients was almost twice as low comparing to dosage given to patients who were *wild type* for all three variants. This is significant for medical practice considering proved predisposition to hypersensitivity in the carriers of abovementioned variants, and keeping in mind that both professional guidelines and producers of acenocoumarol (and other coumarins) demand caution when treating carriers of these variants [9, 12].

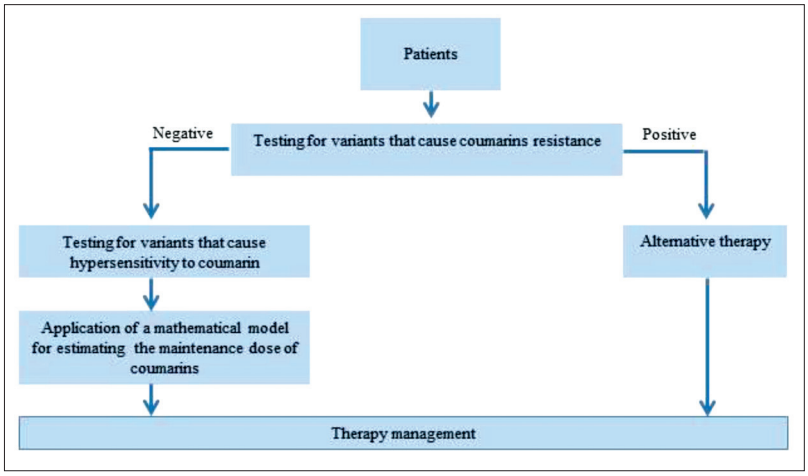

Figure 1. Proposed strategy in the management of anticoagulant therapy, based on pharmacogenetic testing

The results of pharmacogenetic analyses, along with clinical and demographic data, were used for designing and testing mathematical model for predicting individual maintenance dose of acenocoumarol. As expected, in the resulting model, not only did *VKORC1*2*, *CYP2C9*2* and *CYP2C9*3* variants prove to be predictive factors, but also sex, age and weight. In this study, influence of antiarrhythmic drug amiodarone did not show to have significant influence on maintenance dose of acenocoumarol, which is in correlation with predictive model given by other authors, too [15]. On the other hand, there are studies showing amiodarone as a significant factor for assessing maintenance dose of acenocoumarol as well as of phenprocoumon [10]. Such different conclusions may come from factors influencing both the effects of coumarins, and bioavailability and effects of amiodarone. Thus, it has been shown that bioavailability and effect of amiodarone can be modulated by the dietary intake [16]. In addition, there is evidence that certain probiotics can significantly influence pharmacokinetics of this antiarrhythmic [17]. Very often these factors (such as food ingredients) are one of the key differences between populations.

The comparison drawn between prediction model for Serbian population and other algorithms we tested indicates that our model had better prediction than the model given for Dutch population by van Sche et al. [10]. Also, our model had just a slight advantage over the model for Greek population by Markatos et al. [15]. One explanation for such outcome might be geography, i.e., both Greek and Serbian population belongs to Southeast Europe, unlike Dutch population which belongs to Western Europe.

The *VKORC1* variants causing resistance, detected in our study group, are also described by other authors. Resulting amino acid substitutes and their positions in the protein, point to functional significance of these variants.

Change His28Gln is detected in a patient with achieved therapeutic INR value (maintenance dose of acenocoumarol was 60 mg per week). In fact, His28Gln is a change with milder resistance effect, which had been previously elaborated by Czogalla et al. [18]. Change Asp36Tyr is listed as the most often detected substitution in patients with resistance to coumarin. The study conducted by Watzka et al. [19] concerning *VKORC1* variants causing acenocoumarol resistance, showed that this variant represented a quarter of all changes found in the *VKORC1* enzyme. In the majority of patients who were carriers of the Asp36Tyr substitution, the therapeutic value of INR was achieved [19]. In our study change Asp36Tyr was detected in one patient and therapeutic INR was reached with 57 mg of acenocoumarol per week. Substitutions Ala26Pro, Val54Leu, Trp59Arg, Trp59Leu Trp59Cys, Ile123Asn and Leu128Arg are situated in conserved regions of VKORC1 enzyme and their presence leads to significant changes in VKORC1 function. The potential of these substitutions to induce coumarin resistance has been confirmed by a number of authors [9, 18, 19].

In terms of variants which causing resistance, it was not possible to perform appropriate statistical analyses related to probability theory, due to the sample size. Descriptive analysis showed that all carriers of detected *VKORC1* variants showed resistance to acenocoumarol; 75% of them had complete resistance and it was necessary to introduce a different kind of anticoagulant. This is a significant piece of data since timely recognition of patients predisposed to resistance to the drug offers possibility to avoid the risks of trial-and-error method.

Pharmacogenetic algorithms, which are proposed for coumarin therapy, contains genetic variants that are associated with sensitivity but not with drug resistance. Thus, variants causing resistance are being neglected in pharmacogenetic protocols and they are omitted in prospective study or trials. It can be assumed that this practice leaves room for outliers and influences final interpretation of results. That may be one of the reasons that the use of pharmacogenetic algorithms, very often, does not give an advantage over traditional treatment [20, 21]. In accordance

with the above, improved strategy in the management of anticoagulant therapy can be presented as in Figure 1.

Study weakness

This study was based on an analysis of variants of only two genes. Also, in this context, they can be mentioned limited number of patients, the impossibility of conducting a prospective study or the trial study.

CONCLUSIONS

In conclusion, our results suggest that population-specific pharmacogenetic model shows advantages over models that would be used in a generalized manner. Additionally, protocols for the use of coumarins, should not have only mathematical formulas based on genetics factors related to sensitivity, but also testing to *VKORC1* variants causing resistance.

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Варијанте гена *VKORC1* и *CYP2C9* као фармакогенетички фактори у терапији аценокумаролом код болесника у Србији – разматрање преосетљивости и резистенције

Љиљана Ракићевић[1], Мирјана Ковач[2,3], Драгица Радојковић[1], Милица Радојковић[2,4]

[1]Универзитет у Београду, Институт за молекуларну генетику и генетичко инжењерство, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Институт за трансфузију крви Србије, Београд, Србија;
[4]Универзитетски клиничко-болничких центар „Доктор Драгиша Мишовић – Дедиње“ , Београд, Србија

САЖЕТАК

Увод/Циљ Терапија кумаринима представља један од најбољих модела за примену фармакогенетике. Допринос фактора који утичу на терапију кумаринима може значајно да варира између етничких група, што оправдава спровођење студија специфичних за популацију.

Циљ ове студије је био да се анализира утицај најважнијих генетичких фактора (гени *VKORC1* и *CYP2C9*) који утичу на терапију кумаринима код болесника из Србије.

Методе Спроведена је ретроспективна студија која је обухватила 207 болесника на терапији аценокумаролом. Генетичке анализе су вршене директним секвенцирањем. Анализиран је утицај на дозу аценокумарола варијанти (*VKORC1*2*, *CYP2C9*2*, *CYP2C9*3*) које изазивају преосетљивост и варијанти гена *VKORC1* које изазивају резистенцију на кумарине. Вишеструка регресиона анализа је коришћена у циљу дизајнирања математичког модела за предвиђање индивидуалне дозе лека на основу клиничко-демографских и генетичких података.

Резултати Студија је потврдила значајан утицај анализираних генетичких фактора на одржавање дозе аценокумарола. Дизајниран је математички модел за предвиђање индивидуалне дозе аценокумарола и његов некориговани *R*2 је био 61,8. Приликом тестирања, наш модел је дао *R*2 вредност од 42,6 и показао боље предвиђање у поређењу са моделом који су дали други аутори. Код анализираних болесника пронађено је девет различитих варијанти у кодирајућем региону гена *VKORC1*. Међу носиоцима ових варијанти 78% је било потпуно резистентно, те није било могуће постићи терапеутски ефекат чак ни са високим дозама аценокумарола.

Закључци Популациони модел за предвиђање индивидуалне дозе аценокумарола може показати предности у односу на моделе који се користе на генерализован начин. Такође, *VKORC1* варијанте које изазивају резистенцију на кумарин треба узети у обзир приликом планирања терапије.

Кључне речи: фармакогенетика; деривати кумарина; аценокумарол; *VKORC1*; *CYP2C9*

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The potential role of interleukin-6, endotoxin, and C-reactive protein as standard biomarkers for acute appendicitis in adults

Saša Dimić[1], Ivana Dimić[2], Zlatan Elek[1,3], Milan Radojković[4]

[1]Kosovska Mitrovica Clinical Hospital Centre, Department of General Surgery, Kosovska Mitrovica, Serbia;
[2]Kosovska Mitrovica Clinical Hospital Centre, Department of Laboratory Diagnostics, Kosovska Mitrovica, Serbia;
[3]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[4]University of Niš, Faculty of Medicine, Niš Clinical Center, Clinic for Digestive Surgery, Niš, Serbia

SUMMARY

Introduction/Objective Acute appendicitis (AA) is by far the most frequent urgent condition in abdominal surgery and numerous biomarkers may help the physician to diagnose and even predict the severity of the disease.

The objective of the paper was to determine the accuracy of C-reactive protein (CRP), interleukin-6, and endotoxin level and compare it with the diagnostic value of Alvarado score (AS) in adults surgically treated for AA.

Methods Sixty-seven patients were diagnosed with AA using AS. Prior to surgery serum levels of inflammatory biomarkers were determined and together with AS were respectively compared to the results of histopathological analysis of specimens. The patients were divided into three group according to the histopathological assessment.

Results The univariate analysis revealed that the increase of CRP level by one unit increases the probability of complicated AA (CoAA) occurrence by 1% (1.00–1.02, $p < 0.05$). ROC curve analysis has revealed that CRP has better capacity to predict suppurative AA (SAAs)/CoAAs than catarrhal AA (CAA), with the cut-off value of 19.45. The increase of AS value by one unit produced 2.98-fold increase of the probability of CoAA occurrence (1.60–5.57, $p < 0.001$), while positive AS value increases the probability of CoAA occurrence 24.67 times (4.94–123.12; $p < 0.001$). ROC curve analysis demonstrated that AS may predict CoAAs better than CAAs/SAAs, with the cut-off value of 8.50.

Conclusion AS and CRP should be routinely used combined as powerful tools for the diagnosis and prediction of complicated AA.

Keywords: biomarkers; acute appendicitis; adults

INTRODUCTION

Acute appendicitis (AA) is by far the most frequent urgent condition in abdominal surgery with reported lifetime risk of 8.6% in men and 6.7% in women [1]. If the initial inflammation progresses is left untreated, the appendix becomes gangrenous and perforates, causing peritonitis and abscess formation, ileus sepsis, and eventually death. This so-called "complicated appendicitis" occurs in approximately 16.5% of patients [2]. Open or laparoscopic appendectomy remains the standard treatment for the condition. However, despite its high incidence, accurate preoperative diagnosis of AA is still challenging. The negative appendectomy rate is 20.6% [2], with peaks in certain categories of patients such as women in childbearing age (30–50%) or young children (30–46%) [3, 4]. The diagnosis of AA is still predominantly clinical, with 80% diagnostic accuracy of the initial algorithm consisting of suggestive history, pain at McBurney's point and leukocytosis [5]. The addition of imaging methods such as ultrasound and especially computerized tomography (CT) increases the diagnostic accuracy and decreases negative appendectomy rate to 10% [6]. Nevertheless, some serious drawbacks limit the diagnostic utility of these radiological modalities. These include high cost and radiation of CT and low sensitivity of ultrasound (failure of appendix visualization in up to 55% of cases) [7, 8].

Numerous biomarkers are associated with AA and may help the physician to diagnose and even predict the severity of the disease. Some of the routinely used biomarkers are widely available but have insufficient diagnostic value [9], while some newly introduced with higher accuracy require costly and time-consuming analysis. When solely used, not a single one of them has all the desired features, which include good diagnostic accuracy and relatively cheap, simple, and time-sparing assay. Therefore, the combination of biomarkers or their use as a part of stratification scores such as the Alvarado score (AS) in conjunction with history data and examination results may improve their sensitivity [10, 11], although the reliability of these scores is limited due to the interpretation subjectivity of history data and examination findings [12]. The aim of this

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Correspondence to:
Saša DIMIĆ
Anri Dinana 10
38220 Kosovska Mitrovica
Serbia
dimicssasa@hotmail.com

study was to determine the accuracy of inflammatory biomarkers C-reactive protein (CRP), interleukin-6 (IL-6), and endotoxin and compare it with the diagnostic value of AS in adults surgically treated for AA.

METHODS

The study, done in accord with standards of the institutional committee on ethics, included 67 patients that underwent surgery for AA during a period of six months, from January to June 2019 at the Emergency Unit, Niš Clinical Center. There were 35 men (52.2%) and 32 women (47.8%), their median age being 38.7 16.5 years (range: 19–80 years). The patients were diagnosed with AA using AS (Table 1) with diagnostic cut-off value of 6 [13]. Histopathological diagnosis of removed appendices was considered definitive. Prior to surgery, their blood samples were taken and serum levels of CRP, IL-6, and endotoxin were determined. The levels of these inflammatory biomarkers and AS were respectively compared to the results of histopathological analysis of specimens. Surgical treatment of the examined patients included open appendectomy. The severity of appendiceal inflammation was categorized according to the histopathological assessment as presented in Table 2. Gangrenous appendicitis and periappendiceal abscess were categorized as complicated AA (CoAA), as opposed to catarrhal (CAA) and suppurative (SAA) inflammation.

Table 1. Alvarado score for diagnosing acute appendicitis

Clinical signs	Alvarado score
Moving pain	1
Loss of appetite	1
Nausea and vomiting	1
Tension in the right lower quadrant	2
Bloomberg's sign	1
Fever	1 (> 37.2°C)
Leukocytosis (> 10 × 109)	2
Polymorphonuclear > 75%	1
Total	10

Table 2. The severity of acute appendicitis according to the histopathological assessment

Severity grade	Histopathology
Catarrhal appendicitis	Intraluminal polymorphonuclear neutrophils
Suppurative appendicitis	Mucosal infiltration with inflammatory cells
Gangrenous appendicitis (CoAA)	Muscular layer infiltration with inflammatory cells
Periappendiceal abscess (CoAA)	Periappendiceal infiltration with inflammatory cells

CoAA – complicated acute appendicitis

Statistical data processing

The data are presented in the form of an arithmetic mean and a standard deviation, or in the form of absolute and relative numbers. Group comparisons were performed using the Student's t-test or Mann–Whitney U-test. Analysis of variance (ANOVA) was used to compare continuous variables of three independent groups, including subsequent post hoc tests (Tukey method and Tamhane's T2 test). Alternatively, Kruskal–Wallis test was also used. Assessment of the relationship between categorical variables was done using Pearson's χ^2 test. Diagnostic features of the analyzed parameters (sensitivity and specificity, i.e., predictive value) were assessed using receiver operating characteristic curve (ROC) analyses. P-values < 0.05 were considered statistically significant. Statistical analyses were done using SPSS, Version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

According to age, the patients ranged 18–80 years, with no statistically significant difference in sex representation (numerical sex ratio 1.09 in favor of men) (Figure 1). In terms of age and sex distribution, the largest number of patients who were operated on was in the age group 18–29 years, while the least patients were in the age group of 70 years and older (Table 3).

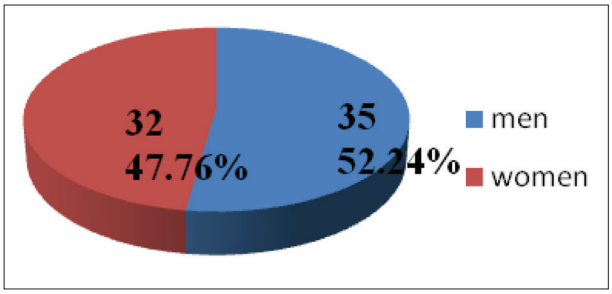

Figure 1. Patients' sex distribution

Table 3. Distribution of different histopathological categories of acute appendicitis in relation to patients' age and sex

Age	18–29y	30–39y	40–49y	50–59y	60–69y	+70y	Σ
Sex	M F	M F	M F	M F	M F	M F	M F
CAA (n = 16)	3 5	2 0	2 0	3 0	0 0	0 1	8 8
SAA (n = 33)	6 7	8 3	1 2	1 1	1 2	0 1	17 16
CoAA (n = 18	2 1	4 1	0 4	0 2	4 0	0 0	10 8
Σ	11 13	12 6	3 6	4 3	5 2	0 2	35 32
	24	18	9	7	7	2	67

CAA – catarrhal acute appendicitis; SAA – suppurative acute appendicitis; CoAA – complicated acute appendicitis

The distribution of AS values among our patients is presented in Figure 2. Sixty-one patients (91%) had AS values compatible with the diagnosis of AA (6 or greater).

The average value of AS in the examined group of patients was 7.94 ± 1.82, with a median of 8.00, with the lowest value of 2 and the highest 10. CRP values on the total sample ranged 0.6–415.2 mg/L, with an average value of 60.37 ± 79.18 mg/L. In the total sample, the average endotoxin values were 3.42 ± 1.20 MU/mL, with the lowest value of 2.88 MU/mL and the highest of 3.72 MU/mL, with a median of 3.28 MU/mL. IL-6 values ranged 13.17–98.83 pg/mL, with a mean value of 91.40 ± 139.63 pg/mL and a median of 31.33 pg/mL (Table 4).

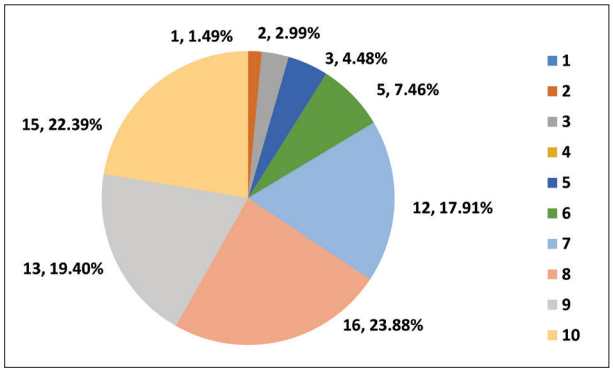

Figure 2. Distribution of Alvarado score values among our patients

Table 4. Mean values of examined parameters

Parameter	X ±SD	Me	Min	Max
Age (years)	38.72 ± 16.46	36	18	80
Alvarado score	7.94 ± 1.82	8	2	10
Endotoxin (MU/mL)	3.42 ± 1.2	3.28	2.88	3.72
IL-6 (pg/mL)	91.40 ± 139.63	31.33	13.17	98.83
CRP (mg/L)	60.37 ± 79.18	29.7	0.6	415.2

X – mean value; SD – standard deviation; Me – median; Min – minimum; Max – maximum

Table 5. Mean values of examined parameters in relation to Alvarado score values

Parameter	Alvarado score negative (5 and less)	Alvarado score positive (6 and more)	p
Age (years)	35.95 ± 16.14 (33)	**42.57 ± 16.42 (39)**	0.0580
Endotoxin (MU/mL)	3.49 ± 1.26 (3.32)	3.32 ± 1.12 (3.17)	0.7029
IL-6 (pg/mL)	37 ± 65.62 (16.5)	**167.16 ± 177.12 (84.83)**	0.0000***
CRP (mg/L)	42.94 ± 64.46 (18.2)	**84.65 ± 91.79 (52.05)**	0.0054**

X – mean value; SD – standard deviation; Me – median;
*p < 0.05;
**p < 0.01;
***p < 0.001 (Student's t-test or Mann–Whitney U-test)

Table 6. Mean values of examined parameters in relation to histopathological findings

Parameter	CAA (n = 16)	SAA (n = 33)	CoAA (n = 18)	p
Age (years)	35.00 ± 17.91 (29)	36.94 ± 15.94 (35)	**45.28 ± 15.12^{ab*} (46)**	0.0570
Alvarado score	6.94 ± 1.18 (7)	7.7 ± 2.05^{a*}	**9.28 ± 0.83^{a***b***} (9)**	0.0000***
Endotoxin (MU/mL)	3.1 ± 0.68 (3.09)	**3.8 ± 1.48^{ac*} (3.39)**	3 ± 0.68 (3.11)	0.0409*
IL-6 (pg/ml)	43.73 ± 90.65 (15.41)	50.6 ± 70.68^{a**} (19.9)	**208.56 ± 197.68^{ab***} (124.58)**	**0.0000*** **
CRP (mg/L)	19.51 ± 27.77 (15.35)	56.35 ± 70.68^{a**} (29.9)	**104.05 ± 103.11^{a***b*} (70.15)**	**0.0002*** **

X – mean value; SD – standard deviation; Me – median; CAA – catarrhal acute appendicitis; SAA – suppurative acute appendicitis; CoAA – complicated acute appendicitis;
Parameters are given as X ± SD and Me;
[a]*vs* CAA
[b]*vs*. SAA;
[c]*vs*. CoAA;
*p < 0.05;
**p < 0.01;
***p < 0.001 (ANOVA, Kruskal–Wallis test, Student's t-test, Mann–Whitney U-test)

AS positive (6 and more) and histopathological (HP) finding were used as the two most authoritative measures in the final diagnosis of AA. Table 5 shows the basic descriptive indicators of the examined continuous variables for AS negative (5 and less) and AS positive. In the group of patients with AS positive, statistically significantly higher values of IL-6 (p < 0.001) and CRP (p < 0.01) were found.

The basic descriptive indicators of the examined continuous variables in relation to the HP finding of AA are given in Table 6. Statistically significant differences were found between the examined groups of parameters – AS, IL-6, CRP (p < 0.001) and for endotoxin (p < 0.05). The value of AS was statistically significantly higher in CoAA in relation to CAA (p < 0.001) and SAA (p < 0.01), and it was statistically higher in SAA in relation to CAA (p < 0.05). IL-6 in CoAA was statistically significantly higher compared to SAA and CAA alone (p < 0.001). CRP was statistically significantly higher in CoAA compared to CAA (p < 0.001), but also SAA (p < 0.05), while the value in SAA was statistically significantly higher compared to CAA (p < 0.01). Endotoxin values were higher in SAA, compared to CAA, but also in CoAA (p < 0.05). By comparing the values of parameters between the groups, it was determined that the subjects with CoAA were statistically significantly older than those with CAA, as well as those with SAA (p < 0.05).

Table 7 shows the findings of the incidence of elevated values of examined parameters in relation to AS. In the group of patients with AS positive, there was a statistically significantly higher presence of HP findings of CoAA (p < 0.001) and IL-6 (p < 0.01). No patient with AS positive had IL-6 values < 5.9 pg/mL.

Statistically significant different representation of findings compared to HP finding of AA was found for IL-6, CRP (p < 0.01) and endotoxin (p < 0.01). The prevalence of AS, IL-6, and CRP findings above the reference values is the highest in CoAA and the lowest in CAA, while the finding of endotoxin above the reference values is most prevalent in SAA. By comparing the values of the examined parameters between the groups with HP findings of AA, it was found that the findings of AS positive were statistically more prevalent in CoAA compared to SAA and catarrhal findings separately (p < 0.001) (Table 8).

Univariate logistic regression analysis for modelling event probabilities was applied in order to assess whether examined parameters may predict the severity of appendiceal inflammation definitively determined by histopathological analysis (Table 9). Positive correlation was found for AS and CRP: an increase of CRP value by one unit increases the probability of CoAA occurrence by 1% (1.00–1.02, p < 0.05); an increase of AS value by one unit produced 2.98-fold increase of the probability of CoAA occurrence (1.60–5.57, p < 0.001), while positive AS value increases the probability of CoAA occurrence 24.67 times (4.94–123.12; p < 0.001). Diagnostic potential (sensitivity and specificity) of these two parameters (CRP and AS) was assessed using ROC curve analysis and two cut-off values were determined: one for the distinction between CAAs

Table 7. The incidence of elevated values of examined parameters in relation to Alvarado score

Parameter	Value	Alvarado score (%)		p
		negative	positive	
Endotoxin	normal elevated	64.1 35.9	75 25	0.3466
IL-6	normal elevated	30.77 69.23	0 **100**	**0.0013****
CRP	normal elevated	17.95 82.05	14.29 85.71	0.7506
Histopathology	CAA and SAA CoAA	94.87 5.13	42.86 **57.14**	0.0000***

CAA – catarrhal acute appendicitis; SAA – suppurative acute appendicitis; CoAA – complicated acute appendicitis;
**p < 0.01;
***p < 0.001 (χ^2 test)

Table 8. The incidence of elevated values of examined parameters in relation to histopathological findings

Parameter	Value	Histopathology (%)			p
		CAA	SAA	CoAA	
Alvarado score	normal elevated	93.75 6.25	66.67 33.33	11.11 **88.89ab*****	**0.0000*****
Endotoxin	normal elevated	81.25 18.75	51.52 **48.48a*c*****	88.89 11.11	**0.0105***
IL-6	normal elevated	43.75 56.25	15.15 84.85	0 **100a****	**0.0050****
CRP	normal elevated	43.75 56.25	12.12 87.88a*	0 **100a****	**0.0018****

CAA – catarrhal acute appendicitis; SAA – suppurative acute appendicitis; CoAA – complicated acute appendicitis;
[a]*vs.* CAA;
[b]*vs.* SAA;
[c]*vs.* CoAA;
*p < 0.05;
**p < 0.01;
***p < 0.001 (χ^2 test)

Table 9. Results of univariate logistic regression analysis assessing the probability of AA histopathology prediction by examined parameters

Parameter	OR	Limits 95% CI		p
		Lower	Upper	
AS	2.98	1.60	5.57	**0.0006*****
Positive AS value	24.67	4.94	123.12	**0.0001*****
CRP	1.01	1	1.02	**0.0165***
Elevated CRP	-	0	-	0.9987

AS – Alvarado score; OR – odds ratio (between catarrhal acute appendicitis and suppurative acute appendicitis on one side and complicated acute appendicitis on the other); CI – confidence interval;
*p < 0.05;
**p < 0.01;
***p < 0.001

and SAAs/CoAAs, and the other for the distinction between CAAs/SAAs and CoAAs. Based on the values of the parameters, it is evident that in this case, slightly better

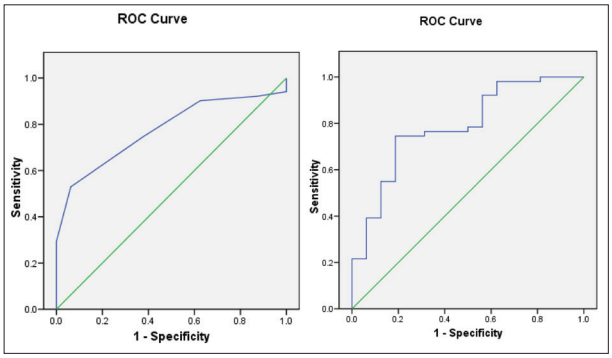

Figure 3. Receiver operating characteristic (ROC) curve analysis presenting predictive features of a) Alvarado score and b) CRP for distinction between catarrhal acute appendicitis and suppurative acute appendicitis / complicated acute appendicitis

Table 10. Receiver operating characteristic curve coordinates presenting predictive features of Alvarado score (AS) and C-reactive protein (CRP) for distinction between catarrhal acute appendicitis and suppurative acute appendicitis / complicated acute appendicitis

AS	Se	Sp	Se + Sp	CRP	Se	Sp	Se + Sp
4	0.941	0.000	0.941	16.3	0.765	0.688	1.452
5.5	0.922	0.125	1.047	17.3	0.745	0.688	1.433
6.5	0.902	0.375	1.277	18.6	0.745	0.750	1.495
7.5	0.745	0.625	1.370	**19.45**	**0.745**	**0.813**	**1.558**
8.5	**0.529**	**0.938**	**1.467**	20.75	0.725	0.813	1.538
9.5	0.294	1.000	1.294	22.15	0.706	0.813	1.518
11	0.000	1.000	1.000	23.7	0.686	0.813	1.499

Se – sensitivity; Sp – specificity

diagnostic characteristics are shown by CRP in comparison to AS. The area under the curve is 0.787, with a standard estimation error of 0.065, with a statistical significance of p = 0.0006 (p < 0.001). The cut-off value is 19.45. Although it has a slightly wider confidence interval (0.659–0.914) compared to AS, it has significantly more sensitivity (74.51), with slightly less specificity and greater overall accuracy (Figure 3, Tables 10 and 11).

On the other hand, it was demonstrated that AS may predict CoAAs better than CAAs/SAAs. The area under the curve is 0.823 with a standard estimation error of 0.053, with a statistical significance of p = 0.0001 (p < 0.001). The cut-off value is 8.50. It has a relatively narrow confidence interval (0.719–0.927), the best ratio of sensitivity and specificity (88.89% and 75.51%, respectively), the highest values of positive predictive value and negative predictive value and overall accuracy, with slightly lower specificity and higher overall accuracy (Figure 4, Tables 12 and 13).

Table 11. Diagnostic features of Alvarado score (AS) and CRP for distinction between catarrhal acute appendicitis and suppurative acute appendicitis / complicated acute appendicitis

Parameter	Area below ROC curve (95% CI)	SE	p	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)	OA (%)
AS	0.775 (0.662–0.889)	0.053	0.0001***	8.5	52.94	93.75	96.43	37.5	62.69
CRP	0.787 (0.659–0.914)	0.065	0.0006***	19.45	74.51	81.25	92.68	44.83	76.12

ROC – receiver operating characteristic; CI – confidence interval; SE – standard error; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; OA – overall accuracy; CRP – C-reactive protein
*p < 0.05;
***p < 0.001

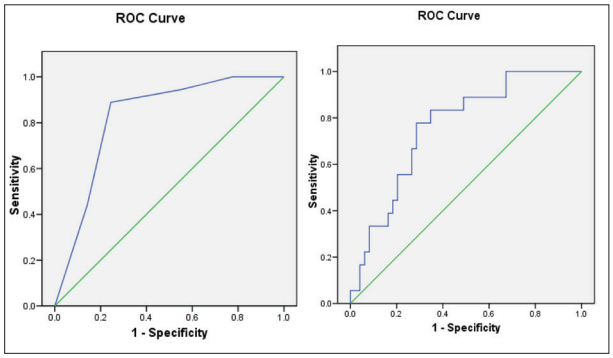

Figure 4. Receiver operating characteristic (ROC) curve analysis presenting predictive features of a) Alvarado score and b) C-reactive protein for distinction between complicated acute appendicitis and catarrhal acute appendicitis / suppurative acute appendicitis

Table 12. Receiver operating characteristic curve coordinates presenting predictive features of Alvarado score (AS) and C-reactive protein (CRP) for distinction between complicated acute appendicitis and catarrhal acute appendicitis / suppurative acute appendicitis

AS	Se	Sp	Se + Sp	CRP	Se	Sp	Se + Sp
4	1.000	0.061	1.061	32.35	0.778	0.653	1.431
5.5	1.000	0.122	1.122	33.95	0.778	0.673	1.451
6.5	1.000	0.224	1.224	35.55	0.778	0.694	1.472
7.5	0.944	0.449	1.393	**40.4**	**0.778**	**0.714**	**1.492**
8.5	**0.89**	**0.760**	**1.644**	45.25	0.667	0.714	1.381
9.5	0.444	0.857	1.302	47.9	0.667	0.735	1.401
11	0.000	1.000	1.000	49.5	0.611	0.735	1.346

Se – sensitivity; Sp – specificity

DISCUSSION

Despite the constant high frequency of AA, its timely and accurate diagnosis may still be elusive. A wide variety of biomarkers has been shown associated with AA and potentially able to reduce the risk of misdiagnosed inflammation and/or negative appendectomy. While traditional markers such as leukocytes are cheap and have relatively poor diagnostic accuracy, some of the novel ones such as IL-6 have been shown to have a higher predictive value, but are more expensive and time-consuming. Thus, the quest for the ideal biomarker to be used solely or combined with other parameters or as a part of stratification scores has been in focus for quite a while now.

IL-6 is a proinflammatory cytokine, mediator of acute phase reaction, and is secreted during inflammatory process and neutrophil recruitment following the invasion of bacteria to the appendix [14, 15]. Some of the previous studies have shown its relatively high sensitivity (73–84%) and low specificity (46–72%) for diagnosing AA and even higher sensitivity (up to 91%) and lower specificity (37%) for diagnosing perforated appendicitis [16, 17]. Elevated serum IL-6 levels were found in the majority of our patients (55, 82.09%, $p < 0.001$). In relation to AS, in our study serum IL-6 levels were significantly both higher ($p < 0.001$) and more frequently elevated ($p < 0.01$) in patients with positive AS values as compared to ones with negative AS (Tables 5 and 7, respectively). Also, in relation to histopathology, IL-6 levels were significantly both higher ($p < 0.001$) and more frequently elevated ($p < 0.01$) in patients with CoAA in comparison to the ones with CAA/SAA (Tables 6 and 8, respectively). However, univariate logistic regression analysis failed to demonstrate the predictive capacity of IL-6 for the severity of appendiceal inflammation. These results are consistent with available literature data reporting good overall performance of IL-6 in terms of sensitivity, but still not specific enough especially for diagnosing CoAA and associated with higher cost and time consuming [18].

CRP is synthesized in the liver as an acute-phase reactant to infection or inflammation. Its serum levels rapidly increase within the first 12h from the onset of symptoms, which is followed by an equally fast normalization. CRP is reported as a useful tool for the diagnosis of AA with its high serum levels indicating suppurative and gangrenous evolution of the inflammation or appendiceal perforation. Multiple studies have demonstrated its high sensitivity (93.6–96.6%) [19–21]. However, it reportedly lacks specificity and cannot be used to distinguish between sites of infection [22]. Elevated serum CRP levels were also found in the majority of our patients (56, 83.58%, $p < 0.001$). In relation to AS, in our study, serum CRP levels were significantly higher ($p < 0.01$) in patients with positive AS values as compared to ones with negative AS (Table 5). However, in contrast to IL-6, although elevated CRP levels were more frequent in patients with positive AS than in those with negative AS, this difference lacks statistical significance (Table 7). In relation to histopathology, CRP levels were significantly both higher ($p < 0.001$) and more frequently elevated ($p < 0.01$) in patients with CoAA in comparison to those with CAA/SAA (Tables 6 and 8, respectively). Also, as opposed to IL-6, univariate logistic regression analysis has demonstrated the capacity of CRP to predict the severity of appendiceal inflammation: it was shown that the increase of CRP level by one unit increases the probability of CoAA occurrence by 1% (1.00–1.02, $p < 0.05$) (Table 9). Furthermore, ROC curve analysis has revealed that CRP has better capacity to predict SAAs/CoAAs than CAA, with the cut-of value of 19.45 (Figure 3, Tables 10

Table 13. Diagnostic features of Alvarado score (AS) and C-reactive protein (CRP) for distinction between complicated acute appendicitis and catarrhal acute appendicitis / suppurative acute appendicitis

Parameter	Area below ROC curve (95% CI)	SE	p	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)	OA (%)
AS	**0.823 (0.719–0.927)**	**0.053**	**0.0001****	**8.5**	**88.89**	**75.51**	**57.14**	72.55	**79.1**
CRP	0.789 (0.638–0.879)	0.062	0.0013**	40.4	77.78	71.43	50	66.04	73.13

ROC – receiver operating characteristic; CI – confidence interval; SE – standard error; Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; OA – overall accuracy;
*$p < 0.05$;
**$p < 0.01$

and 11). These results clearly demonstrate that CRP levels contribute the precise AA diagnosis, the prediction of the severity of inflammation, and may serve as independent markers for CoAAs. Nevertheless, as not specific for AA, its interpretation during the decision-making process should be combined with the analysis of additional diagnostic parameters.

Since AA is a bacterial infection, it may be expected that the severity of inflammation is dependent on the amount of a range of extracellular products and cell-wall constituents produced and released by bacteria. These products stimulate the local and systemic inflammatory response eventually leading to the sepsis and shock. Among these products, endotoxin (lipopolysaccharide complex from the outer membrane of Gram-negative bacteria such as *Escherichia coli*, *Salmonella*, *Shigella*, *Pseudomonas*, *Neisseria*, *Haemophilus influenzae*, *Bordetella pertussis* and *Vibrio cholera*) is one of the most important ones. During an infectious disease, endotoxins released from bacterial cells significantly contribute to the disease pathophysiology and symptoms' development. However, elevated serum endotoxin levels were found in only 21 (31.34%) of our patients. In our study, serum endotoxin levels did not corelate to AS values, i.e., were not significantly neither higher nor more frequently elevated in patients with positive AS values as compared to those with negative AS (Tables 5 and 7, respectively). In relation to histopathology, endotoxin levels were significantly both higher ($p < 0.05$) and more frequently elevated ($p < 0.05$) only in patients with SAA in comparison to the ones with both CAA and CoAA (Tables 6 and 8, respectively). Univariate logistic regression analysis failed to demonstrate the predictive capacity of endotoxin for the severity of appendiceal inflammation. These results of our study indicate a rather modest pathogenic activity of endotoxins and, hence, their smaller diagnostic value. In comparison to bacterial exotoxins, endotoxins are less potent, less specific in their action, and remain stable within the cell membrane until its disintegration during the first hours of bacterial infection. This may explain their relatively low serum levels in patients with CAAs. Also, endotoxins stimulate natural immunity and proinflammatory activity (production of cytokines, activation of the complement and coagulation cascades) [23], thus preventing their high levels in patients with CoAA.

AS enables risk stratification in patients presenting with abdominal pain suspected of AA [13]. However, although AS is often sufficient when probability of AA is intermediate and physician is in doubt, further investigations (ultrasound, CT) or additional biomarkers determination are recommended [24]. In our study, 61 patients (91%) had AS values compatible with the diagnosis of AA (6 or greater). In relation to histopathology, AS values were significantly both higher ($p < 0.001$) and more frequently elevated ($p < 0.001$) in patients with CoAA in comparison to those with CAA/SAA (Tables 6 and 8, respectively). On univariate logistic regression analysis it was shown that an increase of AS value by one unit produced 2.98-fold increase of the probability of CoAA occurrence (1.60–5.57, $p < 0.001$), while positive AS value increases the probability of CoAA occurrence 24.67 times (4.94–123.12; $p < 0.001$) (Table 9). On ROC curve analysis, it was demonstrated that AS may better predict CoAAs than CAAs/SAAs, with the cut-off value of 8.50 (Figure 4, Tables 12 and 13). These data illustrate very good predictive capacity of AS, especially for determining the possibility of CoAA. This is consistent with the results of other researchers reporting AS as a supreme diagnostic aid [25].

CONCLUSION

The present study has demonstrated excellent and complementary diagnostic features of both AS and CRP, especially their capacity for predicting complicated forms of AA. Despite good sensitivity and overall performance, IL-6 was not shown useful due to the lack of specificity for diagnosing CoAA, higher cost, and its time consumption. Endotoxin levels were not significantly elevated in our patients and showed rather modest pathogenic activity and, hence, an insignificant diagnostic value. AS and CRP should be routinely used combined as powerful tools for diagnosing and predicting complicated AA.

Conflict of interest: None declared.

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Потенцијална улога интерлеукина-6, ендотоксина и Ц-реактивног протеина као стандардних биомаркера акутног апендицитиса код одраслих

Саша Димић[1], Ивана Димић[2], Златан Елек[1,3], Милан Радојковић[4]

[1]Клиничко-болнички центар Косовска Митровица, Одељење опште хирургије, Косовска Митровица, Србија;
[2]Клиничко-болнички центар Косовска Митровица, Одељење лабораторијске дијагностике, Косовска Митровица, Србија;
[3]Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;
[4]Универзитет у Нишу, Медицински факултет, Клинички центар Ниш, Клиника за дигестивну хирургију, Ниш, Србија

САЖЕТАК

Увод/Циљ Акутни апендицитис (АА) најчешће је ургентно стање у абдоминалној хирургији, а бројни биомаркери могу помоћи лекару да дијагностикује, чак и предвиди тежину болести.

Циљ рада је био да се утврди тачност Ц-реактивног протеина (ЦРП), интерлеукина-6 (*IL*-6) и ендотоксина и упореди са дијагностичком вредношћу Алварадо скора (АС) код одраслих болесника хируршки третираних због АА.

Методе Код 67 болесника дијагностикован је АА коришћењем АС. Пре операције одређени су нивои инфламаторних биомаркера у серуму и заједно са АС су поређени са резултатима хистопатолошке анализе узорака. Болесници су према хистопатолошком налазу подељени у три групе.

Резултати Униваријантна анализа открила је да повећање нивоа ЦРП за једну јединицу повећава вероватноћу јављања компликованог АА (*CoAA*) за 1% (1,00 до 1,02, $p < 0,05$). Анализа *ROC* кривуље открила је да ЦРП има бољи капацитет за предвиђање супуративних АА (*SAA*)/*CoAAs* у односу на катаралне АА (*CAA*), са *cut-off* вредношћу од 19,45. Повећање вредности АС за једну јединицу довело је до 2,98 пута веће вероватноће појаве *CoAA* (1,60 до 5,57, $p < 0,001$), док позитивна вредност АС (6 и више) повећава вероватноћу појаве *CoAA* 24,67 пута (4,94 до 123,12; $p < 0,001$). Анализа *ROC* кривуље је показала да АС може боље предвидети *CoAAs* него *SAAs/CAAs*, са *cut-off* вредношћу 8,50.

Закључак АС и ЦРП треба рутински користити у комбинацији, као снажне параметре за дијагнозу и предвиђање компликованих АА.

Кључне речи: биомаркери; акутни апендицитис; одрасли

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Squamous cell skin carcinoma due to chronic sacrococcygeal diseases

Serdar Gumus[1], Mehmet Onur Gul[1], Ismail Cem Eray[2], Ibrahim Tabakan[3], Ahmet Rencuzogullari[2], Orcun Yalav[2]

[1]Cukurova University, Faculty of Medicine, Department of Surgical Oncology, Adana, Turkey;
[2]Cukurova University, Faculty of Medicine, Department of General Surgery, Adana, Turkey;
[3]Cukurova University, Faculty of Medicine, Department of Plastic, Reconstructive and Aesthetic Surgery, Adana, Turkey

SUMMARY

Introduction/Objective Sacrococcygeal region squamous cell cancers (SCC) due to chronic sacrococcygeal diseases of skin are rare malignancies. The anatomical relation with the anus represents a challenge for diagnosis and surgical treatment. The oncological treatment algorithm is still controversial.
Here, we investigated the clinicopathologic features of skin cancer of the sacrococcygeal region in a total of 10 cases from a surgical oncology reference center.

Methods We retrospectively analyzed the patients who underwent surgery for sacrococcygeal region skin SCC between January 2010 and July 2020.

Results All patients were male, and the mean age was 52.9 ± 10.5 years. In the etiology, five patients had hidradenitis suppurativa, two had human papillomavirus-associated condyloma (Buschke–Lowenstein tumor), and three had pilonidal sinus disease. The mean time between the development of the lesion and malignancy diagnosis was 21.7 ± 5.8 years. In the preoperative evaluation, three patients had bone invasion. None of the patients had anal sphincter or rectal invasion. Also, no patient had lymph node metastasis or distant metastasis. Wide local excision (WLE) was performed in all patients, with three of them with bone resection. Adjuvant chemoradiotherapy was applied to five patients. In 28.5±13.7 months follow-up, local recurrence occurred in five patients and WLE was performed again in these patients. Of these five patients, two eventually became metastatic. Finally, three patients died due to the disease and six patients are still disease free.

Conclusion Sacrococcygeal region SCCs may rarely develop after a long interval from hidradenitis suppurativa, pilonidal sinus disease, and condyloma acuminata. Anal sphincter-sparing WLE can be applied, but sphincter dysfunction may occur. The disease is associated with a high risk of relapse and poor survival.

Keywords: hidradenitis suppurativa; human papillomavirus; pilonidal sinus disease; skin cancer; sacrococcygeal region

INTRODUCTION

Skin cancers of the sacrococcygeal region due to chronic sacrococcygeal diseases are extremely rare and are frequently seen in the fourth–sixth decade of life [1]. Most of the non-melanocytic skin cancers seen in these anatomical regions are squamous cell cancers (SCC), and fewer are basal cell cancers. Chronic wound scars-, hidradenitis suppurativa- (HS), pilonidal sinus disease- (PSD), human papillomavirus- (HPV) related lesions, and giant condyloma acuminata (Buschke–Lowenstein tumor) are known etiological causes [2, 3, 4]. Patients often suffer from chronic sacrococcygeal diseases. Cancer symptoms are not specific; therefore, the diagnosis is often late.

Malignant transformation of the sacrococcygeal chronic diseases is rare, and treatment approaches are controversial [3]. The common characteristic of sacrococcygeal region SCCs is that the high anatomical close relation of anus and sphincter structures represents a challenge for diagnosis and surgical treatment. Most of the presentations in the literature are case reports, and there are no randomized controlled studies. In this study, we aimed to present the characteristics and outcomes of the malignant transformation of benign sacrococcygeal disease to SCC.

METHODS

We retrospectively reviewed 10 patients who underwent surgery due to sacrococcygeal region skin SCC between January 2010 and July 2020.

Patient evaluation

A detailed physical examination was performed for all patients, and routine digital rectal examination and rectosigmoidoscopy were performed. Magnetic resonance imaging (MRI) was preferred to evaluate the tumor's relationship with the anal canal, anal sphincter, and sacrococcygeal bone structures. The diagnosis was made by incisional biopsy in all cases. Endoanal ultrasonography (EUS) was

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Correspondence to:
Serdar GUMUS
Cukurova University
Department of Surgical Oncology
01330 Sarıcam, Adana
Turkey
seredargumus@hotmail.com

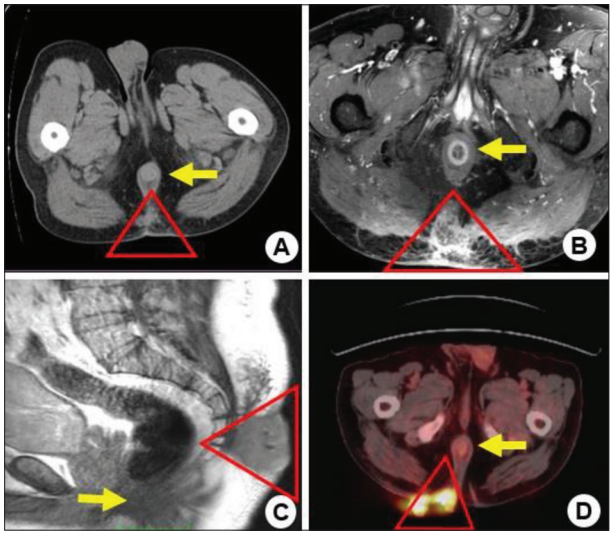

Figure 1. Preoperative radiological images (red triangles show tumors, yellow arrows show anal canal structures); A: preoperative computed tomography image of the tumor in the perianal region; B: preoperative axial MRI image of the perianal tumor; C: preoperative sagittal MRI image of the gluteal tumor; D: preoperative PET-CT image of the tumor located in the gluteal location

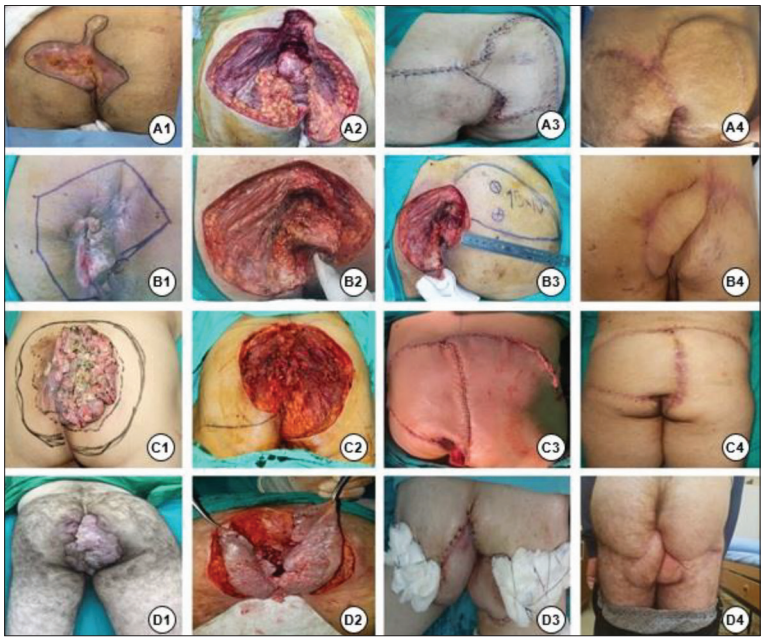

Figure 2. Perioperative images of patients (A, B, C, and D are separate patients); A1, B1, C1, D1: pre-resection tumor appearances; A2, B2, C2, D2: surgical area views; A3, B3, C3, D3: reconstruction procedures; A4, B4, C4, D4: the appearances at long-term follow-up

performed in cases with continued suspicion of sphincter invasion. Thoracoabdominal computed tomography was performed in all the patients to exclude distant metastases. Positron emission tomography / computed tomography (PET-CT) was used when there had been distant and inguinal lymph node metastasis suspicion (Figure 1). Core biopsy was performed from the inguinal lymph node when nodal metastases were suspected. HPV was investigated by a polymerase chain reaction in paraffin-embedded biopsy material taken from all the patients.

Treatment algorithm

In the interdisciplinary tumor board, the patients' individual treatment plans were evaluated, and it was decided to perform wide local excision (WLE) first for all the patients due to non-metastatic disease (Figure 2). A diversion colostomy (loop sigmoidostomy) was performed in cases where tumors were close to the anal canal. Adjuvant chemotherapy (CT) and radiotherapy (RT) were added to cases with surgical margins closer than 1 cm and, if the perineural invasion was identified, in tumors larger than 5 cm.

Data collection

Clinical findings, etiological factors, treatment strategies, histopathological features, and oncological results were examined. Complications were evaluated according to Clavien–Dindo classification (CD) [5, 6]. Recurrences and metastases were determined during the follow-up. Mean survival and disease-free survival times were determined.

Statistical analysis

The data were analyzed using mean, median, minimum, and maximum values. The follow-up time was defined from surgery to death or the last patient contact.

Ethical approval

This study was approved by the Ethics Committee of the University of Cukurova Faculty of Medicine, Adana, Turkey (reference number: 99/11, date: 15.05.2020) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients for future studies when they were operated on.

RESULTS

Patient characteristics

The clinical characteristics of the patients are given in Table 1. All patients were male, and their mean age was 52.9 ± 10.5 years (range: 39–68 years). In etiology, five patients had HS, two patients had HPV, and three patients had PSD. In six patients, tumors were located at the gluteal region and in four at the perianal margin. One patient had previously undergone surgery for a perianal abscess and one for PSD. The mean time between the development of the lesion and malignancy diagnosis was 21.7 ± 5.8 years. This period was 26.6 ± 2.4 years in HS cases, 15.6 ± 4 years in PSD, and 14.1 ± 2.1 years in HPV. No patient had anal sphincter or rectal invasion; however, three patients had bone invasion. No patient had distant metastasis in the preoperative

Table 1. Our series of 10 cases of HS, HPV, and PSD complicated by SCC

Case	Age (years)	Etiology	Interval (years)	Location	Previous surgery	Bone invasion
1	53	PSD	12	Gluteal	Pilonidal sinus surgery	Yes
2	52	HS	26	PA margin	Abscess drainage	Yes
3	39	HPV	20	PA margin	No	No
4	40	HPV	17	Gluteal	No	No
5	55	HS	25	PA margin	No	Yes
6	68	HS	28	Gluteal	No	No
7	39	HS	30	PA margin	No	No
8	64	HS	24	Gluteal	No	No
9	60	PSD	20	Gluteal	No	No
10	59	PSD	15	Gluteal	No	No

PA – perianal; PSD – pilonidal sinus disease; HS – hidradenitis suppurativa; HPV – human papillomavirus

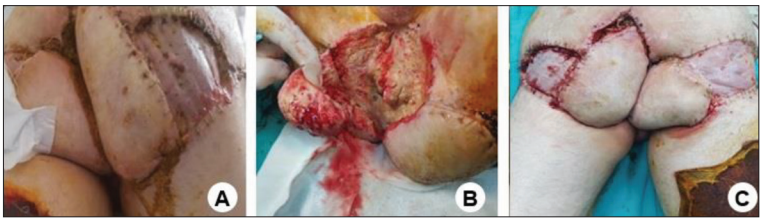

Figure 3. Appearances of flap failure; A: flap failure in the early postoperative period due to fecal contamination; B: flap separation (the patient is in the supine position); C: repeated flap reconstruction after fecal control is achieved

evaluation. Only one patient had inguinal lymph nodes with high SUV-max values on PET-CT. However, it was reactive lymphadenopathy, according to the histopathology examination of the core biopsy.

Treatment

Surgical margins were confirmed with the frozen section, and all of WLE was R0. A diversion colostomy was performed in four patients at the first surgery. Two patients underwent coccygectomy, and one patient had sacrectomy (below S5) with coccygectomy. After resection, the defects that occurred were closed in nine patients by reconstruction performed by plastic and reconstructive surgeon. Only one patient had a CD-3b complication as flap dehiscence requiring reoperation (Figure 3). Postoperative chemo radiotherapy (CRT) was applied to five patients (Table 2). Finally, in three patients, the diversion colostomy never closed and became permanent due to sphincter dysfunction.

Pathological findings

Well-differentiated SCC in eight patients and verrucous SCC (Buschke–Lowenstein

Table 2. Operative and follow-up characteristics of patients

Case	Surgery	Reconstruction	CD	Postoperative CRT	Time of relapse (months) and treatment	Permanent colostomy	Metastasis	Follow-up (months)	Outcome
1	WLE, below S5 sacrectomy, coccygectomy	SAPF	1	No	No	No	No	48	Death
2	WLE, coccygectomy	SAPF	2	CT: 5 FU, cisplatin RT: 4600 cGy TS	13 mo.: WLE, VY FLAP 42 mo.: WLE, below S4 sacrectomy, coccygectomy, colostomy	Yes	Yes (44 mo.)	44	DDD
3	WLE, colostomy	V-Y flap	3b	CT: 5 FU, cisplatin RT: 4800 cGy TS	10 mo.: WLE, RF 14 mo.: WLE, below S4 sacrectomy, coccygectomy	No	No	39	Alive
4	WLE, colostomy	RF	1	CT: 5 FU, mitomycin C RT: 4500 cGy TS, 1440 cGy Bost	8 mo.: WLE, SAPF	No	No	28	Alive
5	WLE, coccygectomy, colostomy	PTF	2	CT: 5 FU, cisplatin RT: 4800 cGy TS	8 mo.: WLE, RF	Yes	No	14	DDD
6	WLE	SAPF	2	No	No	No	No	25	Alive
7	WLE, colostomy	SAPF	2	CT: 5 FU, mitomycin C RT: 3600 cGy TS, 900 cGy PLN	9 mo.: WLE, RF 27 mo.: WLE	Yes	Yes (30 mo)	39	DDD
8	WLE	V-Y flap, RF	1	No	No	No	No	14	Alive
9	WLE	SAPF	1	No	No	No	No	8	Alive
10	WLE	Primer close	1	No	No	No	No	26	Alive

CRT – chemo radiotherapy; CT – chemotherapy; RT – radiotherapy; WLE – wedge local excision; RF – rotation flap; PTF – posterior thigh flap; CD – Clavien–Dindo complication score; SAPF – superior artery perforating flap; DDD – death due to disease; TS – tumor side; PLN – pelvic lymph nodes

Table 3. Histopathological results of patients

Case	Histopathology	Surgical margin (mm)	Perineural invasion	Tumor size (mm)
1	WD SCC	10	No	45 × 27 × 10
2	WD SCC	2	Yes	50 × 35 × 20
3	Verrucous SCC	20	No	100 × 80 × 10
4	Verrucous SCC	8	No	120 × 15 × 10
5	WD SCC	5	No	50 × 40 × 30
6	WD SCC	10	No	45 × 30 × 20
7	WD SCC	15	Yes	70 × 60 × 20
8	WD SCC	10	No	30 × 12 × 10
9	WD SCC	15	No	35 × 32 × 20
10	WD SCC	17	No	35 × 24 × 22

WD – well differentiated; SCC – squamous cell cancers

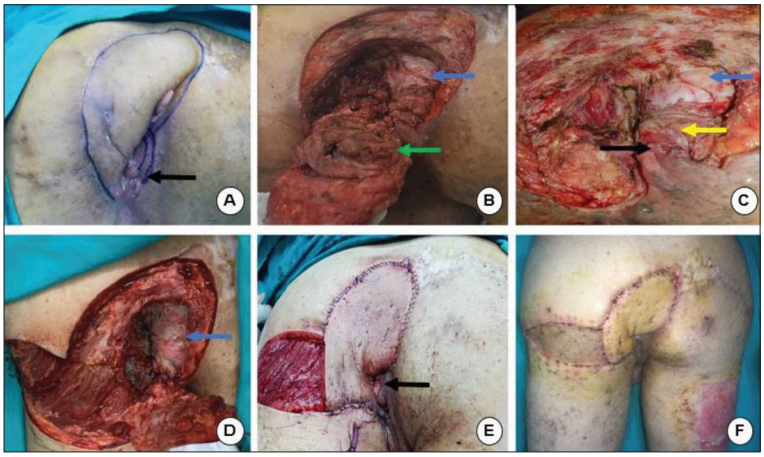

Figure 4. Local recurrence appearances; A: pre-resectional appearances (the black arrows point to the anal verge); B: un-bloc resection with sacrectomy and coccygectomy (the blue arrows point to the distal rectum, and the green arrow points to resected bone); C: surgical area views after resection (the yellow arrow points to the anal sphincter structures); D: rotational flap preparation from the left gluteal area; E: anal verge after reconstruction; F: postoperative appearance

tumor) in two patients were detected. Surgical margin was less than 1 cm in three patients (cases 2, 4, and 5), and perineural invasion was observed in two of the patients (cases 2 and 7). Five patients had tumors larger than 5 cm (cases 2, 3, 4, 5, and 7) (Table 3).

Follow-up

In the follow-up period, local recurrence occurred in five patients. The first relapse occurred within an average of 9.6 ± 2 months. A second WLE was performed on these patients (Figure 4). Local recurrence occurred again in three of these five patients and WLE was performed for the third time. In a mean follow-up of 28.5 ± 13.7 months, four patients died (three due to the disease, one due to myocardial infarction), and six patients are still disease-free (Table 2).

DISCUSSION

In this study, we aimed to present our treatment experiences on skin SCCs that develop from the sacrococcygeal region due to chronic sacrococcygeal diseases, which is rare cancer. The treatment algorithm is not clear in guidelines such as National Comprehensive Cancer Network [7, 8]. Although we are a reference center in surgical oncology and colorectal surgery, we could only present a small number of patients due to the rarity of the disease. However, this study shows that the disease is associated with high recurrence and poor prognosis.

It is known that HS, HPV, and PSD may rarely be an etiologic factor of SCC [2, 3, 4]. Anderson and Dockerty [9] first described malignant degeneration of HS in 1958. The incidence of developing SCC from HS is 1–3.2%. Although HS is more common in women, malignant transformation has been reported more frequently in men [10]. In our series, five patients had HS, and as noted in the literature, all of these patients were male.

Human papillomavirus, another known etiological factor of SCC, is associated with many cancers including head, neck, anal, vulvar, penile, and vaginal carcinomas [11, 12]. The tumor that develops in the perianal region due to HPV is named Buschke–Lowenstein tumor. Clinically, it presents as exophytic, fungal masses with raised morphology. It has benign appearance on histopathology but is locally destructive. It carries a high recurrence rate and a significant potential for malignant transformation [4, 13]. In our series, HPV-associated SCC was detected in two patients.

Another known predisposing disease is PSD and malignant degeneration can occur in approximately 0.1% of patients with untreated PSD [14, 15]. The malignant degeneration process is believed to be similar to pilonidal squamous cell carcinomas and other chronic inflammatory wounds such as burns, osteomyelitis, scars, skin ulcers, and fistulas [2]. Actually, malignant degeneration mechanisms of HS and PSD are still not fully known. It is believed to result from the release of free oxygen radicals by activated inflammatory cells. Genetic damage caused by these radicals is thought to induce neoplastic transformation. In addition, it is claimed that disruption of standard DNA repair mechanisms due to chronic inflammation may play a role in the development of malignancy [16].

The patients with sacrococcygeal SCC usually have chronic perianal or gluteal wounds in their medical history. The cancer symptoms are nonspecific and can be confused with those of the current chronic disease. There may be a long interval between the development of benign illness to cancer. Therefore, the diagnosis is often delayed [17, 18]. According to Kohorst et al. [3], the time from HS to SCC was 28.5 years. In our series, the mean time between the development of the lesion and the diagnosis of malignancy was 21.7 ± 5.8 years, and it was longer in cases with HS than in others.

The treatment strategy of SCC may vary depending on the size of the tumor, the invasion status, and the condition of the complications that may develop (such as fecal incontinence) [18]. Mohs micrographic surgery technique can be used in clinical practice for the treatment of SCC. It is a special form of skin cancer surgery in which the surgeon and pathologist work together. This technique is important in cosmetically (and functionally) sensitive anatomical locations [19]. However, this is not applicable in large and deep invasive tumors such as we have presented in our series.

Abbass and Valente [20] described the treatment algorithm of perianal margin SCC as follows: (i) WLE with 1 cm clear margin should be performed in T1N0 lesions (< 2 cm) without anal sphincter invasion; (ii) T2N0 lesions (2–5 cm) without lymph node involvement can be treated with WLE; however, since the risk of lymph node involvement can be as high as 25%, CRT can be applied; (iii) lymph node-positive patients or T3, T4 patients, should be treated with combined modality CRT as mentioned above, as well as radiotherapy, including the pelvis and bilateral inguinal lymph nodes. In our series, we applied an algorithm similar to that of Abbass and Valente [20] and we applied chemoradiotherapy to tumors larger than 5 cm. In addition, we added adjuvant therapy in cases with perineural invasion. Because perineural invasion is an independent risk factor for lymph node and distant metastases. It has also been associated with lower survival [21]. In our series, the patients with perineural invasion had become metastatic. Also, two-thirds of the patients who died due to the disease in this series had perineural invasion.

According to some authors, routine lymphatic dissection may be more beneficial than CRT for inguinal lymph node metastasis [18]. However, there are no randomized controlled studies on the effect of this on survival. The role of elective lymphatic dissection in high-risk SCC remains undefined with most studies limited to head and neck primary sites. On the other hand, sentinel lymph node (SLN) biopsy is seen as an unproven and yet theoretically appealing surgical technique to accurately stage high-risk SCCs with minimal morbidity, identify the early occult nodal disease, and select patients that might benefit from therapeutic lymphatic dissection or other adjuvant therapy [22]. However, the role of SLN biopsy in these patients remains unclear, as in cases of routine lymphatic dissection. In the present series, only one patient had inguinal lymph nodes with high SUV-max values on imaging. However, it was reactive lymphadenopathy, according to the histopathology of the core biopsy. We think that these lymph nodes are secondary to long-term chronic perianal/gluteal inflammation. Therefore, in the presence of suspected lymph node metastases, core biopsy maybe a guide to avoiding unnecessary routine inguinal dissections.

Sacrococcygeal SCCs can rarely invade the anal sphincter complex [1, 18]. In our series, detailed rectal examination, pelvic MRI, and EUS were used to determine sphincter invasion in cases in which the tumor was close to the anal sphincter complex. In this way, we excluded sphincter or rectal invasion. Although we removed tumors by preserving the anal sphincters and anal canal in all the patients, we would like to state that some open diversion colostomies have become permanent due to the dysfunction of the anal sphincters.

A skin graft may often be required to close the defect after large excision. V-Y flap can often be sufficient. A plastic surgeon's help may be needed to close larger defects [23]. In our series, primary closure was performed in only one patient, reconstruction with flap was required in the others. However, despite loop colostomy, that fecal contamination-related flap failure may develop, as in the third case in our series. Therefore, the option of end colostomy may also be useful in these patients.

In the literature, the local recurrence rate was higher than 50% after SCC resection [24]. Kohorst et al. [3] reported local recurrence in seven of 12 perianal margin SCC cases after WLE. In a total of 4.3 years of follow-up, they lost most of the patients (n = 7) due to the disease. Similarly, the local recurrence rate was high in our series, and three patients died due to cancer, despite receiving CRT. All three of these patients had SCC that developed on the basis of HS. The presence of sinus tracts in HS provides an easy route for malignant cells to spread, and detection of malignant transformation can be difficult against the background of chronic tissue inflammation [25]. The easy spreading or transmission of the malignant cells via sinus tracts may increase the risk of metastasis on HS rather than Buschke–Lowenstein tumor and PSD-based SCC. As seen in the present study, the time between the development of the lesion and malignancy diagnosis is longer in SCCs that develop on the basis of HS. This is an indication of the more insidious course in cases of SCC due to HS. According to the Medline study by Maclean and Coleman [26], the two-year survival rate after SCC diagnosis on the bases of HS was reported to be only 52%. In our series, metastasis and mortality were also seen only in HS cases. In this respect, we can say that HS creates a more aggressive tumor.

Limitations of this study include its retrospective nature and a small number of cases.

CONCLUSION

HS, HPV, and PSD play a role in the development of sacrococcygeal SCC. There may be a long interval between the development of benign illness to cancer. Wide local excision is the most common procedure in treatment. Diversion colostomy and flap reconstruction may be part of surgical treatment. In some cases, CRT may be required, but, unfortunately, there is a high recurrence risk and poor survival despite all treatments.

Conflict of interest: None declared.

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Сквамоцелуларни карцином коже код хроничних болести сакрококцигеалне регије

Сердар Гумуш[1], Мехмет Онур Гул[1], Исмаил Џем Ерај[2], Ибрахим Табакан[3], Ахмет Ренџозогулари[2], Орчун Јалав[2]

[1]Универзитет Чукурове, Медицински факултет, Одељење за хируршку онкологију, Адана, Турска;
[2]Универзитет Чукурове, Медицински факултет, Одељење за општу хирургију, Адана, Турска;
[3]Универзитет Чукурове, Медицински факултет, Одељење за пластичну, реконструктивну и естетску хирургију, Адана, Турска

САЖЕТАК

Увод/Циљ Сквамоцелуларни карциноми коже су ретки малигни тумори сакрококцигеалне регије. Анатомски однос са анусом представља изазов за дијагнозу и хируршко лечење. Алгоритам онколошког лечења је и даље контроверзан.

У нашем истраживању испитали смо клиничко-патолошке особине карцинома коже сакрококцигеалног региона код укупно десет болесника лечених у референтном центру за хируршку онкологију.

Методе Ретроспективно смо анализирали болеснике који су оперисани због сквамоцелуларног карцинома коже сакрококцигеалне регије у периоду од јануара 2010. до јула 2020. године.

Резултати Сви болесници су били мушког пола, просечне старости 52,9 ± 10,5 година. У етиологији, пет болесника је имало супуративни хидраденитис, двојица су имала кондиломе повезане са хуманим папилома вирусом (тумор Бушке–Левенштајн), а тројица болест пилонидалног синуса. Просечно време између развоја лезије и дијагнозе малигнитета било је 21,7 ± 5,8 година. Ниједан болесник није имао инвазију аналног сфинктера или ректума, али су тројица имала инвазију костију у преоперативној процени. Такође, ниједан болесник није имао метастазе у лимфним чворовима или удаљене метастазе. Широка локална ексцизија извршена је код свих болесника, а код тројице је удружена са ресекцијом костију. Адјувантна хеморадиотерапија примењена је код пет болесника. У праћењу од 28,5 ± 13,7 месеци, локални рецидив се десио код пет болесника и широка локална ексцизија је поново изведена. Од ових пет болесника, два су на крају постала метастатска. Коначно, три болесника су умрла због болести, а шест болесника је и даље без болести.

Закључак Сквамоцелуларни карциноми коже сакрококцигеалне регије могу се ретко развити након дугог интервала присуства супуративног хидраденитиса, болести пилонидалног синуса и кондилома акумината. Може се применити широка ексцизија са презервацијом аналног сфинктера, нажалост са могућом дисфункцијом сфинктера. Болест је повезана са великим ризиком од рецидива и лошим преживљавањем.

Кључне речи: хидраденитис супуратива; хумани папилома вирус; болест пилонидалног синуса; рак коже; сакрококцигеална регија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cost effectiveness analysis associated to the treatment of primary open-angle glaucoma according to disease severity

Zoran Velkovski[1], Maja Belevska[2], Biljana Gjorgjeska[3], Jasmina Đorđević-Jocić[4]

[1]Medical University Sofia, Faculty of Pharmacy, Sofia, Bulgaria;
[2]St Kliment Ohridski Bitola University, Clinical Hospital Bitola, Bitola, North Macedonia;
[3]Goce Delčev Štip University, Faculty of Medical Sciences, Štip, North Macedonia;
[4]University of Niš, Faculty of Medicine, Clinic of Ophthalmology, Niš, Serbia

SUMMARY

Introduction/Objective Primary open-angle glaucoma (POAG) treatment should be individually tailored to the disease severity and type, effectiveness and secondary side effects of the medications used. This research aimed to assess the direct medical costs and the cost effectiveness associated with pharmacotherapy in visually impaired people with POAG according to disease severity.

Methods This scientific study is designed as an observational cross-sectional study with a quantitative analytical approach and was conducted in the period from July 2020 to June 2021 on the territory of North Macedonia. The study included 157 patients with binocular POAG in the early, moderate and advanced clinical stage, up to the age of 67, with changes in visual acuity and work ability. During the assessment of the effects of pharmacotherapy were analyzed the types, mutual correlations and effectiveness of the most commonly prescribed antiglaucomatous medications and the cost benefit from their administration. Direct medical costs are calculated according to disease severity in the last 12 months using real-time data of public interest.

Results The beta blockers due to their affordable price and availability are the dominant option with high-cost benefit for primary treatment of POAG. Antiglaucoma medications and diagnostic procedures are major components of direct medical treatment costs.

Conclusion Pharmacotherapy is the dominant alternative compared to other types of treatment because it is safer and is associated with greater effectiveness and lower direct medical costs.

Keywords: pharmacotherapy; direct medical costs; antiglaucoma medications; economic burden

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy which, due to untimely diagnosis and inadequate treatment, leads to irreversible loss of visual acuity [1].

It is most commonly associated with increased intraocular pressure (IOP), but not always and requires lifelong therapy [2].

It has a prevalence of 1–2% in the population over 40 years of age and it is the second most common cause of vision loss and accounts for 13% of global blindness [3].

About 70% of all glaucoma cases are patients with primary open-angle glaucoma (POAG) and female patients are more dominant [2, 4].

Due to long-term treatment, high treatment costs and low-cost effectiveness, glaucoma generates individual and family financial burden [5, 6, 7] and has a huge socio-economic impact on the society and population [8].

Pharmacotherapy with antiglaucoma medications is the safest option for primary treatment of POAG [9].

Surgical treatment performed at an early clinical stage prevents the progression of POAG and has lower or identical direct medical treatment costs compared to pharmacotherapy [10].

Direct medical costs for treatment increase as the disease severity progresses [11, 12, 13], but stagnate or decrease over time [14, 15].

The treatment outcome and the height of direct medical costs are essentially related to timely diagnosis and individual approach to treatment according to disease severity [16].

The untimely diagnosis, irregular control of IOP and visual acuity [6] and low level of patient awareness of the essence of POAG adversely affect the outcome of treatment [17].

This research aimed to assess the direct medical costs and the cost effectiveness associated with pharmacotherapy in visually impaired people with POAG according to disease severity.

METHODS

This scientific study was designed as a cross-sectional observational study with a quantitative analytical approach (cross sectional study) and was conducted in the period July 2020–June 2021 on the territory of North Macedonia.

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Correspondence to:
Zoran VELKOVSKI
Orde Chopela 1
7000 Bitola
North Macedonia
zoranv_mk@yahoo.com

According to inclusion criteria, the study included 157 patients diagnosed with binocular POAG at an early, moderate and advanced clinical stage. The patients were up to 67 years old and treated with pharmacotherapy; whereas the patients in advanced clinical stage were socioeconomically predisposed and with reduced work ability.

The patients' diagnosis was confirmed by ophthalmological examination, while the visual acuity and disease severity (clinical stages) were determined according to ICD 10-CM: 40.11 in early, moderate and advanced clinical stage, in accordance with the classification guidelines of the European Glaucoma Society.

A specially designed questionnaire was used for the analysis of the clinical-demographic parameters, whereas a standardized visual analogue scale EQ VAS was used for self-assessment of the general health status.

The research was carried out during periodic health examinations in the Institute of Occupational Medicine and the Department of Ophthalmology at the University Clinical Hospital Bitola, Department of Ophthalmology at the Medical Faculty Skopje, Department of Ophthalmology at the Medical Faculty Štip and specialist ophthalmological hospitals in several cities in Macedonia.

The assessment of the effects of pharmacotherapy involved the following: type of most commonly prescribed antiglaucomatous medications, their mutual correlations, the effectiveness and the secondary side effects from their use. The effectiveness and outcome of the treatment were analyzed by controlling the height and normalization of the IOP and the preservation of visual acuity in the last 12 months.

Direct medical costs were calculated according to the disease severity in the last 12 months using real-time data of public interest presented by the Health Insurance Fund of North Macedonia and State Statistical Office.

Statistical data processing was performed by descriptive and comparative statistics procedures with SPSS software package version 22.0 for Windows (IBM Corp., Armonk, NY, USA).

The attributive (qualitative) series were analyzed by determining the coefficients of ratio, proportion and rate, and were presented as absolute and relative numbers. Numerical (quantitative) series were analyzed by finding the measures of central tendency (average value; median, minimum and maximum value; interactive range) and dispersion measures (standard deviation and standard error).

Pearson χ^2 test for homogeneity, Fischer exact test and Fisher–Freeman–Halton exact test were used to determine the association between certain variables in the groups of subjects.

The Shapiro–Wilk W test was used to determine the normality of frequency distribution of investigated variables. Risk factors were quantified using probability ratios, odd ratio (OR).

In order to test the significance of the difference between the parameters analyzed, depending on the type and distribution of data, Student's t test for two independent samples, analysis of variance (ANOVA) for multiple independent samples and the non-parametric Mann–Whitney U test and Kruskal–Wallis H test for independent samples were used.

A value of $p < 0.05$ was used to determine significance. The obtained results from the analysis were compared with scientific reference literature in the world and are presented numerically, with tables and figures.

The research was done in accord with standards of the institutional committee on ethics and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

The highest proportion of the patients included in the research were in the initial clinical stage 38.22% and the mean age of the patients was 57.51 ± 6.28 years. (Table 1)

Regarding the demographic parameters, 77.71% of the patients lived in a city; 89.17% in a married community; 50.32% had a secondary education; 43.31% were a clerk/administrator by profession, without statistical significance between the two sexes.

17.91% of the patients had a family history of eye diseases; 21.06% had registered comorbid diseases, while 15.29% were not informed about the essence of POAG.

Table 1. Clinical and demographic characteristics of patients

Parameters	Sex			P Difference test
	Total N = 157 (100%)	Male N = 70 (44.59%)	Female N = 87 (55.41%)	
Disease severity				
Early	60 (38.22%)	27 (45%)	33 (55%)	$\chi^2 = 0.837$; df = 2; p = 0.667
Moderate	52 (33.12%)	23 (44.23%)	29 (55.77%)	
Advanced	45 (28.66%)	20 (44.44%)	25 (55.56%)	
Age	57.51 ± 6.28	57.60 ± 6.10	57.40 ± 6.46	Z = 0.332; p = 0.739
Age when diagnosed	47.53 ± 5.61	47.71 ± 5.51	47.34 ± 5.70	Z = 0.339; p = 0.734
Duration of therapy.	9.54 ± 4.27	9.62 ± 4.12	9.46 ± 4.41	$\chi^2 = 0.235$; df = 2; p = 0.715
Comorbid diseases / N (%)	33 (21.06%)	15 (21.43%)	18 (20.69%)	$\chi^2 = 0.152$; df = 1; p = 0.697
Genetic Predisposition / N (%)	28 (17.91%)	13 (18.57%)	15 (17.24%)	$\chi^2 = 0.002$; df = 1; p = 0.988
Side effects				
Local	35 (22.35%)	16 (22.86%)	19 (21.84%)	$\chi^2 = 0.023$; df = 2; p = 0.989
Systemic	5 (3.16%)	2 (2.86%)	3 (3.45%)	
Health informed / N (%)				
Yes / partially	133 (84.71%)	60 (85.71%)	73 (83.91%)	$\chi^2 = 0.235$; df = 2; p = 0.889
No	24 (15.29%)	11 (15.71%)	13 (14.94%)	

χ^2 – Pearson Chi-square test; Z – Mann–Whitney U test; *significant for $p < 0.05$

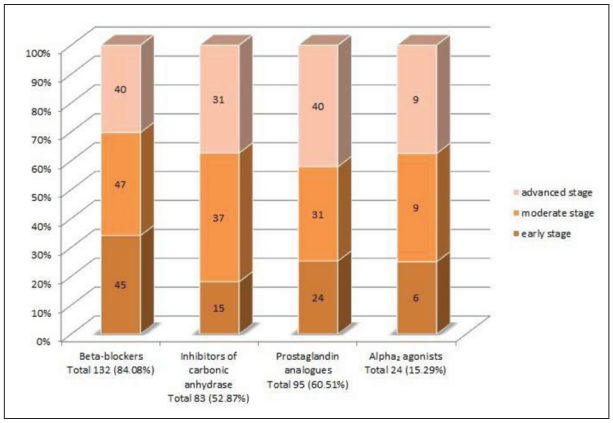

Figure 1. Antiglaucomatous medications prescribed in the treatment

Table 2. Treatment outcome of the patients

Parameters	Treatment Outcome				P Difference test
	Total	Regression	Slow Progression	Worsening	
Treatment Method / N (%)					
Pharmacotherapy / 12 months	157 (100%)	124 (78.98%)	19 (12.1%)	14 (8.92%)	†p = 0.00001*
Adherence to Treatment / N (%)					
Yes	124 (78.98%)	56 (45.16%)	43 (34.68%)	25 (20.16%)	χ^2 = 69.049; df = 2; p = 0.0001*
No	33 (21.02%)	3 (9.09%)	5 (15.15%)	25 (75.76%)	
Treatment outcome according to disease severity / 12 months / N (%)					
Early	60 (38.22%)	51 (85%)	6 (10%)	3 (5%)	†p = 0.00001*
Moderate	52 (33.12%)	41 (78.85%)	6 (11.54%)	5 (9.61%)	
Advanced	45 (28.66%)	32 (71.11%)	7 (15.56%)	6 (13.33%)	

χ^2 – Pearson Chi-square; †Fisher Freeman Halton exact test; *significant for p < 0.05

The patients were treated with pharmacotherapy, with prescription of various anti-glaucomatous medications (Figure 1, Table 2).

The type and method of administration of antiglaucoma medications depend on the disease severity, the level of IOP and their effectiveness. The medications are individually tailored and, in our research, the predominant type of pharmacotherapy were the beta blockers.

In the early stage, the predominant option was mono pharmacotherapy 60%, in the moderate stage, combination therapy of two medications 55.77% and, in the advanced stage, combination therapy of two 33.33% or three or more anti-glaucomatous medications 66.67%.

The effectiveness of pharmacotherapy is manifested by regression, slow progression or worsening of disease severity.

Significant association of with the highest number of regression outcome of the disease was observed in patients in initial (early) when compared to advanced clinical stage, p = 0.00001.

Over 20% of the patients did not adhere to regular treatment due to economic reasons or lack of information and ignorance about the essence of POAG.

Loss of visual acuity and reduced work ability are the reasons for non-fulfillment or poor fulfilment of work responsibilities and eventual relocation of patients to job positions with lower personal income (Table 3).

Considering the fact that this concerned adult population of up to the age of 67, the average self-assessment of the general health status of the patients was low, 7.68 ± 1,56. Of whom, 36.94% due to reduced visual acuity and work ability received a low monthly income of up to 250 euros, without significance between the two sexes, p = 0.316.

Antiglaucoma medications were a major component of direct medical costs 80,86% and imposed an economic burden from 3.05% ± 0.75 to 10.52% ± 0.62, which was significantly associated with patients who received low monthly income (nonparametric ANOVA: F = 6.38; p = 0.0001).

Table 3. Economic burden associated with primary open-angle glaucoma pharmacotherapy

Parameters	Primary open-angle glaucoma severity				P Difference test
	Total	Initial	Moderate	Advanced	
Self-assessment of health condition / EQ VAS Mean/ %	7.68 ± 1.56	8.25 ± 1.19	7.65 ± 1.55	7.15 ± 1.95	†p = 0.00001* advanced / early
Reduced personal income / N (%)	25 (15.92%)	0	8 (5.1%)	17 (10.83%)	†p = 0.00001* moderate / advanced
Monthly personal income / N (%)					
Low ≤ 250 euros	55 (35.03%)	13 (23.64%)	16 (29.09%)	26 (47.27%)	†p = 0.00001*
Direct medical costs / euros					
Monthly	15.13 ± 1.6	6.1 ± 1.2	14.4 ± 1.7	24.9 ± 1.9	1p = 0.00001*
Annual	181.56 ± 19.2	73.2 ± 14.4	172.8 ± 20.4	298.8 ± 22.8	1p = 0.0002*
Types of costs / Mean / %					
Specialist ophthalmological examinations	19.14	25.5	18.89	13.03	χ^2 = 66.752; df = 4; p = 0.00001*
Antiglaucomatous medications	80.86	74.5	81.11	86.97	
Economic burden on low monthly income / %	6.68 ± 0.70	3.05 ± 0.75	6.47 ± 0.73	10.52 ± 0.62	^{1}F = 6.38 p = 0.0001*

1p – Kruskal–Wallis H test; χ^2 – Pearson Chi-square; F – nonparametric ANOVA; †Fisher exact test; *significant for p < 0.05

DISCUSSION

The patients included in the research were aged 40–67, predominated by females 55.41%, while over 50% of the patients were older than 59.

Previous studies show that POAG is most often manifested binocularly with the highest frequency over the age of 60, while 55–60% of the patients are female [2, 4].

POAG is diagnosed between the age of 40–50 in 46.91% of the patients, while in 7.63% younger than 40. According to the available studies, POAG is most often diagnosed after 40 [18], although that limit is gradually lowering to a younger age under 40 years old [19].

Of the registered comorbid conditions, 33.33% were due to diabetes mellitus and the rest to hypertension, cardiovascular and metabolic diseases and were 2.47 times more common in patients with advanced stage [OR = 2.47 (1.20–5.07) 95% CI].

In total, 84.71% were fully/partially informed about the essence of POAG, but not all of them, without statistical significance between the two sexes, p = 0.195.

Studies conducted in Egypt and Nigeria showed that 40–50% of illiterate and uninformed people had been treated for glaucoma [6, 13].

Antiglaucoma medication of choice in the treatment of POAG were beta blockers (Thymolol) which were administered in 132 cases (84.08%), and their alternative were analogues of prostaglandins 95 (60.51%), carbonic anhydrase inhibitors 83 (52.87) %) and alpha$_2$ agonists 24 (15.29%), which are prescribed as mono or combination therapy.

Beta blockers were usually prescribed as monotherapy 16.56%, while in combination therapy of two medications, beta blockers and carbonic anhydrase inhibitors 22.29%, and in combination of three medications, beta blockers, carbonic anhydrase inhibitors and prostaglandin analogues 30.57%. Combined use of more than one antiglaucoma medication is an effective way to normalize IOP, but it increases the treatment cost and the possibility of secondary side effects [7, 20].

Adverse drug reactions were reported in 40 cases (25.48%). Of these, 23 (14.65%) were secondary local reactions in the form of irritation, allergy, dry eye and eye pain, and secondary cataract in seven cases (4.46%). Of the patients treated with non-selective beta-blockers, five (3.18%) showed complications in the form of primary bronchial asthma, exacerbation of asthma and deviations in functional spirometry tests.

In long-term studies for the treatment of POAG in patients who have used medications with preservatives and non-selective beta-blockers (Thymolol) the following was observed: local adverse drug reactions 12–20% [21] and 2.7%, systemic reactions in the form of bronchial asthma exacerbation [7, 22]. Pharmacotherapy with prostaglandin analogues is the most effective way to normalize IOP and has the highest cost benefit for treatment and the lowest percentage of secondary side effects [20].

The treatment outcome in 78.98% was successful with normalization of IOP and regression of the disease, in 12.10% was partially successful with slow progression, and in 8.92% the outcome was unsuccessful with deterioration and progression of the disease, p = 0.00001, without significance between the two sexes, p = 0.772.

Increased disease severity in the last 12 months has been registered in all clinical stages, 13.33% of whom were patients in advanced clinical stage.

Studies conducted in Egypt and Nigeria report unsuccessful normalization of IOP in glaucoma patients treated with pharmacotherapy 42–50% [6, 13].

21.02% of the patients did not adhere to regular treatment. Of whom, 15.15% were uninformed about the essence of POAG and the benefits of regular treatment, while 84.85% due to economic reasons used generic alternative anti-glaucomatous medications with inadequate dosage.

Many people with POAG are partially blind due to untimely diagnosis [13], poor health care [17] and low levels of health education and awareness, especially in developing countries [5].

Long-term treatment, high medication prices and lack of information about the essence of POAG are most common reasons for patients' non-adherence to medication [16].

In 75.75% of the patients who did not adhere to treatment, the IOP height in the last 12 months was usually higher than 28 mmHg. Patients who adhere to regular treatment have 5.14 times higher chance of a successful outcome compared to patients with irregular treatment [OR = 5.14 (2.36–14.63) 95% CI].

According to several studies in case of unfavorable outcome and increased disease severity, the possibility of non-adherence to medication must be taken into account [23].

Significant association was established between low monthly income and patients in advanced clinical stage, p = 0.00001, without statistically significant association between the sexes, p = 0.955.

There are numerous studies regarding the connection of the advanced clinical stage with the reduced personal income, high treatment costs, decreased visual acuity and low-cost effectiveness for treatment [13, 14, 24].

Monthly and annual direct medical costs for treatment were significantly lower in the initial, whereas the highest in the advanced clinical stage (Kruskal–Wallis H test, p = 0.00001 / 0.0002).

Most of the direct medical costs 80.86% were for antiglaucoma medications which were significantly higher in the advanced clinical stage, p = 0.0001, while similar findings were referred to in other studies related to the economic burden of glaucoma treatment [11, 12].

Treatment costs for patients with advanced clinical stage were 2.4 times higher compared to those for patients with initial stage [OR = 2.4 (9.79–60.93) 95% CI].

Beta-blocker pharmacotherapy is associated with low and prostaglandin analogues with high-cost treatment. Identical cost findings have been reported in other comparative studies of glaucoma treatment with medications [25, 26].

Significantly higher direct medical costs for treatment and low-cost benefit were observed in patients with comorbid conditions/diabetes mellitus, p = 0.00001, compared to other patients.

Patients over the age of 60 have insignificantly higher direct medical costs for treatment, p = 0.0612. Parallel studies on the economic burden of glaucoma treatment have reported a significant association between higher treatment costs, advanced disease severity and older mean age [24].

The Health Insurance Fund of North Macedonia partially subsidizes the costs of non-selective beta-blockers and carbonic anhydrase inhibitors, but not the costs of prostaglandin analogues, other expensive medications and diagnostic procedures used to treat POAG.

Available studies depending on the economic development of the countries indicate annual direct medical costs of 45–809 euros [5, 12, 13, 15, 27].

The burden of direct medical costs on the monthly personal income is significantly higher in patients with advanced clinical stage, who receive low monthly personal income (One Way ANOVA: Av = 6.38; p = 0.0001).

Low-cost effectiveness and individual economic burden on the monthly personal income, from 1.3–61.5%, are referred to in numerous studies conducted in different geographical regions [6, 7, 13].

CONCLUSION

POAG treatment should be individually tailored to the disease severity and type, effectiveness and secondary side effects of the medications used.

Pharmacotherapy is the dominant alternative compared to other types of treatment because it is safer and is associated with greater effectiveness, lower direct medical costs and higher cost effectiveness during treatment.

Beta-blockers, due to their availability and low cost, are the most common option as a primary type of pharmacotherapy in the initial (early) stage of the disease.

The progression of the disease severity is associated with change, intensification of treatment and increased direct medical costs.

Long-term IOP control with the initial treatment without modifications will allow regression of the disease, slow disease progression and reduced treatment costs. Screening programs for early detection of POAG, subsidizing the cost of expensive anti-glaucoma medications and increased awareness of the essence of POAG are essential.

Conflict of interest: None declared.

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Анализа исплативости третмана примарног глаукома отвореног угла према тежини болести

Зоран Велковски[1], Маја Белевска[2], Биљана Ђорђеска[3], Јасмина Ђорђевић-Јоцић[4]

[1]Медицински универзитет Софија, Фармацеутски факултет, Софија, Бугарска;
[2]Универзитет „Св. Климент Охридски“ Битољ, Клиничка болница Битољ, Битољ, Северна Македонија;
[3]Универзитет „Гоце Делчев“ Штип, Факултет медицинских наука, Штип, Северна Македонија;
[4]Универзитет у Нишу, Медицински факултет, Клиника за очне болести, Ниш, Србија

САЖЕТАК

Увод/Циљ Третман примарног глаукома отвореног угла треба да буде индивидуално усаглашен са тежином и врстом болести, ефикасношћу и секундарним нежељеним ефектима коришћених лекова.

Циљ рада је био да се процене директни медицински трошкови и исплативост фармакотерапије код третмана примарног глаукома отвореног угла према тежини болести.

Методе Научни рад је осмишљен као опсервациона студија пресека са квантитативним аналитичким приступом и спроведена је у периоду од јула 2020. до јуна 2021. године на територији Северне Македоније. Студијом је обухваћено 157 пацијената, узраста до 67 година, са бинокуларним примарним глаукомом отвореног угла у раном, умереном и узнапредовалом клиничком стадијуму, са променама видне оштрине и радне способности. Током процене ефеката фармакотерапије анализирани су типови, међусобне корелације и ефикасност најчешће примењиваних антиглаукоматозних медикамената. Директни медицински трошкови у последњих 12 месеци су процењени коришћењем ажурираних података од јавног интереса.

Резултати Бета-блокатори су због своје приступачне цене и доступности доминантна примарна опција са великом исплативошћу у третману примарног глаукома отвореног угла. Антиглаукоматозни лекови и офталмолошки прегледи сачињавају главне компоненте директних трошкова лечења.

Закључак Фармакотерапија је доминантнија у односу на остале видове лечења јер је безбеднија, повезана је са већом ефикасношћу и мањим директним медицинским трошковима.

Кључне речи: фармакотерапија; директни медицински трошкови; антиглаукоматозни лекови; економски терет

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effect of hemodialysis on macular thickness

Vesna Šobot[1], Vesna Jakšić[2,3], Igor Kovačević[1,3], Dragan Lukić[4]

[1]University Clinical Center of Serbia, University Eye Clinic, Belgrade, Serbia;
[2]Zvezdara University Medical Center, Prof. dr Ivan Stanković Clinic for Eye Diseases, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[4]University Clinical Center of the Republic of Srpska, Eye Clinic, Banja Luka, Bosnia and Herzegovina

SUMMARY

Introduction/Objective During hemodialysis (HD) treatment great fluctuations were recorded in the systemic hemodynamic parameters and in the volume and composition of ocular fluid. There are only a few studies that analyzed the effect of HD on retinal and macular thickness with conflicting results. Objective of this study was to determine macular thickness, marked as central foveal thickness, average macular thickness and macular volume, shortly before and after HD.

Methods This prospective study included 30 chronic renal failure (CRF) patients of HD treatment. Thorough ophthalmologic examinations were performed including evaluation of best corrected visual acuity, intraocular pressure and slit-lamp examination of all eye segments. Macular thickness was determined by optical coherence tomography shortly before and after HD. The next parameters were evaluated: central foveal thickness, average macular thickness and macular volume. The correlation between systemic parameters and macular thickness changes during HD was tested.

Results There were significant changes in body weight and blood pressure pre- and post-HD. Results showed macular thickness (central foveal thickness, average macular thickness and macular volume) decreased, but the change was not significant. There was no significant correlation between systemic hemodynamic parameters and macular thickness changes.

Conclusion Results of this study showed there was no statistically significant changes in macular thickness CRF patient undergoing HD. Further research on a larger group of patients and a longer follow-up time are required to confirm these findings.

Keywords: macular thickness; hemodialysis; optical coherence tomography

INTRODUCTION

Most patients with chronic renal failure (CRF) undergo hemodialysis treatment. Although hemodialysis is effective, in the long term it can lead to numerous changes in many patients. The most common eye problems that occur in patients treated with hemodialysis are changes in visual acuity and refraction, dry eye, calcium deposits on the conjunctiva, "band" keratopathy, corneal endothelial damage, and lens clouding [1, 2]. Furthermore, it has been shown that these patients have morphologic and physiologic changes in the retina [3, 4].

During one hemodialysis (HD) session, there are substantial changes in electrolyte concentrations and the volume and distribution of body fluids, which can affect many systemic parameters, as well as the composition and volume of fluid in the eye.

Previous studies have shown that HD has an effect on central corneal thickness and intraocular pressure (IOP), axial length and ocular surface [5, 6, 7]. A very small number of researchers investigated retinal and macular thickness changes during HD. The results of these studies are contradictory. A few studies have shown that HD has an effect on retinal thickness (RT) [8, 9, 10], while in others this effect was not significant [11, 12].

The aim of this study was to determine macular thickness expressed as central foveal thickness (CFT), volume, and average macular thickness immediately before and after hemodialysis.

METHODS

The prospective study enrolled 30 patients who are on a chronic hemodialysis program at the Department of Nephrology of the Clinic for Internal Medicine, Zvezdara Medical Center in Belgrade. The research was conducted from December 2014 to March 2015 at the Prof. Dr. Ivan Stanković Clinic for Eye Diseases, Zvezdara Medical Center. Informed consent was obtained from all patients and the Ethics Committee of the Zvezdara Medical Center approved the study. The patients were enrolled in the study according to the following criteria: patients with CRF treated with hemodialysis and visual acuity greater than 0.1. The exclusion criteria from the study were the presence of opaque optical media and refractive anomalies greater than ± 10 Dsph.

Patients underwent hemodialysis three times a week for three to four hours. It was used standardized dialysate flow rate of 500 ml / min at blood flow rate 250–300 ml / min.

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Correspondence to:
Vesna ŠOBOT
University Clinical Center of Serbia
University Eye Clinic
Pasterova 2
11129 Belgrade
Serbia
vesna.sobot01@gmail.com

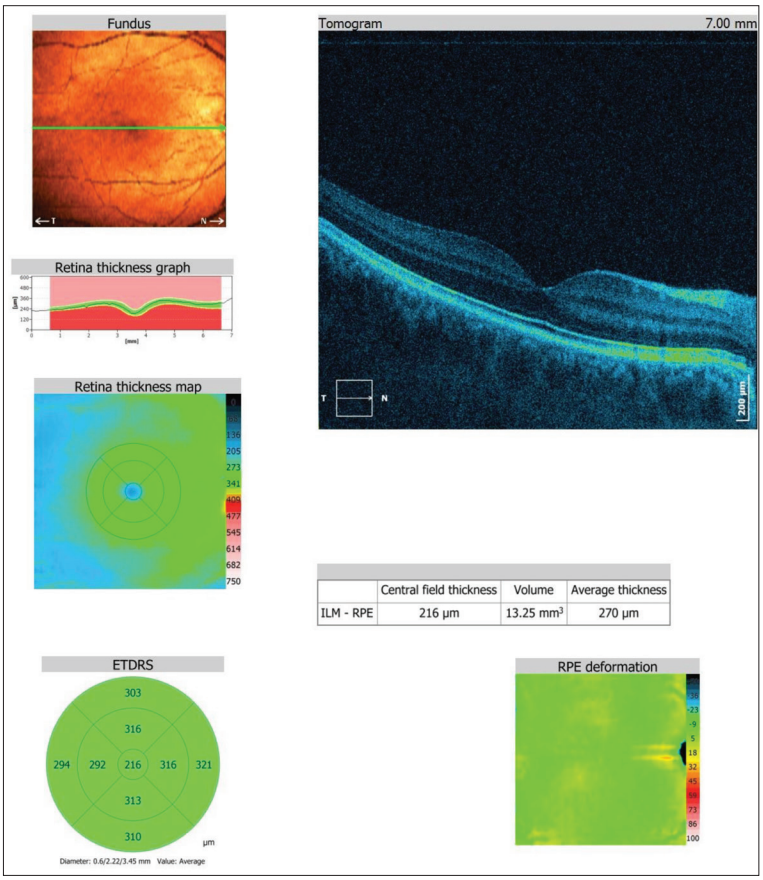

Figure 1. Optical coherence tomography scan with early treatment diabetic retinopathy study retinal thickness map

Table 1. The effect of hemodialysis on blood pressure

Parameters	HD	x̄	SD	med	min	max	p
Systolic blood pressure	before HD	140	26.9	140	80	190	< 0.001
	after HD	116.8	14.9	120	80	140	
Diastolic blood pressure	before HD	74.6	13.7	80	40	110	< 0.001
	after HD	64.7	9.8	65	40	80	
Mean blood pressure	before HD	90	29.2	98.3	0	126.7	< 0.001
	after HD	52	41	78.3	0	100	

HD – hemodialysis; mean blood pressure – (2 × diastolic blood pressure + systolic blood pressure) / 3)

A thorough ophthalmological examination was performed, which consisted of the determination of the best corrected visual acuity, IOP, examination of the anterior and posterior segment of the eye. Snellen optotype was used to determine visual acuity, while IOP was measured using Goldmann's applanation tonometer. Macular thickness was determined by optical coherence tomography (Spectral Domain Optical Coherence Tomography, SD [OCT]; Copernicus HR, Optopol, Zawiercie, Poland) immediately before and after hemodialysis. OCT imaging was performed after the pupils were dilated using local mydriatics (2.5% Sol. Phenylephrin and 1% Sol. Tropicamid). RT was analyzed using data obtained by a map defined by the Early Treatment Diabetic Retinopathy Study [13]. The following were analyzed: inner, intermediate and outer ring of radius 0.6 *vs.* 2.2 *vs.* 3.45 µm. The average RT corresponding to the inner ring is marked as CFT, while the average macular thickness (MEAN) is the average thickness of all three rings. Volume is the volume of the macular region radius 3.45 µm (Figure 1). Blood pressure and body weight were recorded before and after the HD session. Weight change represents the amount of fluid removed by hemodialysis. Standard monitoring parameters (serum concentrations: Ca, P, urea, creatinine, PTH, Fe, Er, ALP; eGFR and Kt / V) are taken from the patient's medical history. Based on the cause of CRF, patients were divided into three groups: hypertensive nephrosclerosis (HTA), diabetes mellitus (DM) and others.

In total, 30 eyes from 30 patients were used for statistical analysis. Which eye (right or left) will be included in the analysis was determined by randomization, except for six patients in whom only one eye met the inclusion criteria. Descriptive statistical methods and methods for testing statistical hypotheses were used for primary data analysis. The t-test for two dependent samples and analysis of variance (ANOVA) were used. Pearson's correlation coefficient was used to examine the correlation of age, HD length, and system parameters with changes of macular thickness. Value $p < 0.05$ was considered statistically significant.

RESULTS

The study included 30 patients (17 men and 13 women). The average age of all subjects in the study was 61.2 ± 11.1 years. The youngest participant had 27 and the oldest 77 years. The causes of CRF in the subjects were hypertensive nephrosclerosis (n = 17), diabetes mellitus (n = 4), while in nine patients the causes were other (chronic pyelonephritis (n = 3), primary glomerulopathies (n = 3), obstructive uropathy (n = 2) and polycystic kidney disease (n = 1).

Changes in arterial blood pressure (systolic, diastolic and mean) before and after hemodialysis was statistically significant. Average values of differences between systolic blood pressure, diastolic blood pressure and mean blood pressure before and after HD were 33.16 ± 19.09 *vs.* 10.53 ± 9.85 *vs.* 38 ± 36.59 mmHg ($p < 0.001$). (Table 1).

The average value of body weight in subjects before HD was 72.1 ± 15.9 kg, while after HD 67.3 ± 20 kg, which is a statistically significant difference ($t = 8.999$; $p < 0.001$). (Table 2). There was no statistically significant correlation

Table 2. The effect of hemodialysis on body weight

Parameters	n	x̄	SD	med	min	max	p
BW before HD	22	72.1	15.9	67.9	53.5	110	
BW after HD	29	67.3	20	66	0	107	
ΔBW	21	2.6	1.2	2.5	0.5	5	< 0.001

BW – body weight; HD – hemodialysis; ΔBW– difference in body weight before and after HD

Table 3. The effect of hemodialysis macular thickness

Parameter	HD		SD	med	min	max	p
CFT	before HD	346	118.4	329.5	175	583	0.142
	after HD	308.3	100.1	300.5	128	545	
MEAN	before HD	280.1	52.1	263.5	199	448	0.734
	after HD	275.1	52.6	269.5	185	398	
Volume	before HD	13.44	2.69	263.5	7.01	21.96	0.347
	after HD	13.17	2.59	269.5	9.06	18.96	

HD – hemodialysis; CFT – central foveal thickness;
MEAN – average macular thickness; Volume – macular volume

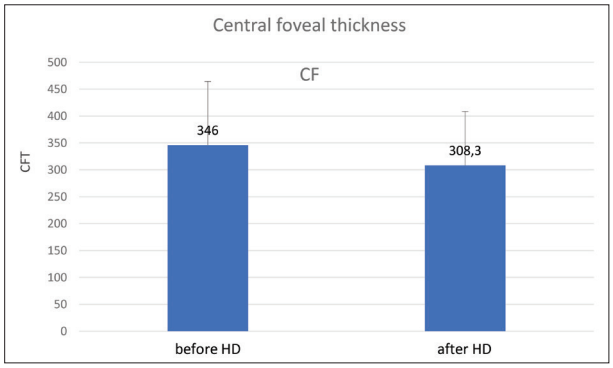

Figure 2. The effect of hemodialysis on central foveal thickness

Table 4. Changes of macular thickness after hemodialysis in groups of patients formed based on CRF causes

Parameter	Group	x̄	SD	min	max	p
ΔCFT	HTA	73.3	131.20	-46	455	0.432
	DM	-7.5	139.82	-216	80	
	Other	7.33	161.17	-272	294	
ΔMEAN	HTA	-1	48.25	-75	88	0.862
	DM	17.25	98.02	-106	131	
	Other	5.89	62.41	-91	93	
ΔVolume	HTA	-0.46	2.56	-5.20	4.31	0.060
	DM	3.44	2.88	0.19	6.44	
	Other	-0.15	3.17	-3.91	4.55	

HTA – hypertensive nephrosclerosis; DM – diabetes mellitus; ΔCFT – difference of central foveal thickness before and after hemodialysis; ΔMEAN –difference of average macular thickness before and after hemodialysis; ΔVolume – difference in macular volume before and after hemodialysis

Table 5. Values of serum concentrations of the examined system parameters

Parameters	n		SD	med	min	max
Ca	30	2.3	0.2	2.2	1.9	2.9
P	30	1.3	0.5	1.4	0	2.4
Urea	30	21.4	4.9	21.5	13.4	31.7
Creatinine	30	835.4	128	809	623	1211
eGFR	30	5.2	1.1	5	3	8
PTH	30	244	265.1	153.8	15.7	1213
Fe	29	10.2	3.8	9.6	3.2	22.6
Er	27	3.2	0.5	3.4	1.8	4.4
ALP	30	83.6	57.6	64.5	28	310
Kt/V	20	1.4	0.3	1.4	0.8	2.2

between patient age and changes in body weight and blood pressure, as well as between length of HD and the above parameters ($p > 0.5$).

The effect of hemodialysis on macular thickness

The mean value of CFT before HD was 346 ± 118.4 μm, while after HD 308.3 ± 100.1 μm. Difference in CFT before and after HD was not statistically significant ($t = 1.514$; $p > 0.05$). Average value of average macular thickness (MEAN) before HD was 280.1 ± 52.1 μm, while after HD 275.1 ± 52.6 μm. The difference in average macular thickness before and after HD was not statistically significant ($t = 0.343$; $p > 0.05$). Average macular volume before HD was 13.44 ± 2.69 mm^3, while after HD was 13.17 ± 2.59 mm^3. The difference in macular volume before and after HD was not statistically significant ($t = 1,347$; $p > 0.05$). (Table 3, Figure 2)

There was no statistically significant correlation between age and macular thickness ($r = 0.079$; $p = 0.689$), HD length and macular thickness ($r = 0.180$; $p = 0.359$), as well as between hemodynamic parameters (ΔBW, ΔBP) and macular thickness ($p > 0.5$).

Change in macular thickness in the examined groups

Mean values of macular thickness changes after HD in groups of patients formed based on CRF causes are listed in Table 4. There were not statistically significant differences in macular thickness before and after HD between groups ($p > 0.05$).

Correlation of system parameters with macular thickness

The average values of serum concentrations of the examined system parameters are given in Table 5. There was no statistically significant correlation between the parameters listed in Table and macular thickness ($p > 0.05$).

DISCUSSION

There was a statistically significant difference between body weight and blood pressure (systolic, diastolic and mean) before and after hemodialysis. The principal goal of hemodialysis is to regulate metabolic disbalance and to remove excessively accumulated fluid. Volume overload is one of the main mechanisms of blood pressure elevation in patients undergoing HD [14]. Therefore, the change in body weight and blood pressure during HD is expected because the difference between body weight before and after HD represents the amount of removed liquids.

The results of this research showed that there was a decrease in the macular thickness, expressed as CFT and average macular thickness, after HD, however this difference was not statistically significant. Furthermore, findings of our study showed there was no statistically significant

correlation between examined systemic parameters and changes in macular thickness. Possible explanation for this result is the mechanisms responsible for maintaining the balance between plasma volume and dynamic changes in fluid volume during HD. Bauer and Brooks [15] showed that, although there is a decrease in the total volume of extracellular fluid during HD, this decrease is present only in the interstitial compartment, while the plasma volume remains unchanged. One of the possible pathophysiological mechanisms that explains this effect represents an increase in colloidal osmotic pressure. Namely, during HD due to fluid loss there is an increase in colloidal osmotic pressure and the creation of a pressure gradient between plasma and interstitial fluids. The pressure gradient causes movement of interstitial fluid to plasma, which maintains the balance between plasma volume and dynamic changes in total fluid volume in patients with HD [16]. It is possible that because of these mechanisms, HD has a low effect on retinal circulation.

The results of research conducted by Sun et al. [11] and Azem et al. [12] are in accordance with the results in this paper. Namely, Sun et al. [11] examined the change in macular thickness, among other parameters, before and after one HD session on 202 patients using OCT. In their research there were no statistically significant changes in macular thickness, although there was a decrease of subfoveal choroidal thickness. Furthermore, in a study conducted by Azem et al. [12] changes in macular thickness were not statistically significant. In both of these studies' methodology was very similar to ours. In contrast to the research above, there are also studies which showed statistically significant reduction in macular thickness after hemodialysis [8, 9]. Studies by Jung et al. [8] and Theodossiadis et al. [9], although methodologically very similar to ours, showed that there was a statistically significant reduction in macular thickness after HD. Based on the obtained results, Theodossiadis et al. [9] concluded that the reduction in macular thickness was more pronounced in patients with clinically significant macular edema. In none of these studies, there was no statistically significant correlation between changes in macular thickness and changes in monitored systemic parameters (body weight and blood pressure), which is complementary to the results presented in this study.

A lot of CRF patients undergoing HD have severe ocular problems involving retina. Proper diagnosing and treating these conditions can be particularly challenging. Knowing how systemic changes influence retinal changes, could help ophthalmologists in clinical practice to correctly interpret diagnostic tests and adequately treat patients. Results of this study showed that there was no significant change of macular thickness during HD, which is valuable information for planning OCT examination which can be done independently of time interval from a HD session.

It is important to note that there were limitations in this research. Total number of 30 patients examined represent an insufficiently large sample and therefore obtained results could not be generalized to all patients with CRF who are on hemodialysis. Moreover, this study examined only the short-term effects of hemodialysis. It is possible the results would be different if patients were examined before and after multiple hemodialysis sessions. Diabetic macular edema is one of the most important causes of vision impairment and it develops mainly due to disruption of blood-retinal barrier and capillary leakage. It is possible that systemic hemodynamic changes during HD have greater influence on macular thickness in diabetic patients. Considering that our study enrolled only four DM patients, further research with more diabetic patients in the study cohort could give us more useful information.

CONCLUSION

The results of this study showed that there was no significant reduction in macular thickness after HD in CRF patients. However, further research with more patients is needed and a longer follow-up period to confirm these results.

Conflict of interest: None declared.

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Утицај хемодијализе на дебљину макуле

Весна Шобот[1], Весна Јакшић[2,3], Игор Ковачевић[1,3], Драган Лукић[4]

[1]Универзитетски клинички центар Србије, Клиника за очне болести, Београд, Србија;
[2]Клиничко-болнички центар Звездара, Клиника за очне болести „Проф. др Иван Станковић", Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија;
[4]Универзитетски клинички центар Републике Српске, Клиника за очне болести, Бања Лука, Босна и Херцеговина

САЖЕТАК

Увод/Циљ У току једне сесије хемодијализе (ХД) долази до великих промена системских хемодинамских параметара, као и састава и волумена течности која се налази у оку. Постоји мали број студија, са опречним резултатима, које су испитивале утицај ХД на дебљину ретине и макуле. Циљ ове студије је био одређивање дебљине макуле, исказане као централна фовеална дебљина, просечна дебљина макуле и укупан волумен макуларне регије, непосредно пре и после ХД.

Методе У проспективну студију укључено је 30 болесника са хроничном бубрежном инсуфицијенцијом који су на лечењу ХД. Обављен је детаљан офталмолошки преглед укључујући одређивање најбоље кориговане видне оштрине, интраокуларног притиска, преглед предњег сегмента ока и очног дна. Дебљина макуле је одређивана оптичком кохерентном томографијом непосредно пре и после ХД. Параметри праћења су били централна фовеална дебљина, просечна дебљина макуле и укупан волумен макуларне регије.

Резултати Постојала је статистички значајна разлика између телесне тежине и крвног притиска пре и после ХД, тј. дошло је до значајног смањења наведених параметара после ХД. Резултати овог рада су показали да је након ХД дошло до смањења дебљине макуле, исказане као централна фовеална дебљина, просечна дебљина макуле и укупан волумен макуларне регије, међутим та разлика није била статистички значајна. Није било статистички значајне корелације између испитиваних системских параметара и промене дебљине макуле.

Закључак Резултати овог рада су показали да нема значајног смањења дебљине макуле након ХД код болесника са хроничном бубрежном инсуфицијенцијом. Међутим, неопходна су даља истраживања са већим бројем болесника и дужим периодом праћења која би потврдила ове резултате.

Кључне речи: дебљина макуле; хемодијализа; оптичка кохерентна томографија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Efficacy of intravenous immunoglobulin in the treatment of a COVID-19 patient

Maja Stojanović[1,2], Milan Marković[2], Dubravka Đinović[2], Slobodan Popović[2], Jela Borovinić[3]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Zvezdara University Medical Center, Department of Anesthesiology and Intensive Care, Belgrade, Serbia;
[3]Zvezdara University Medical Center, Department of Supply of Blood and Blood Products, Belgrade, Serbia

SUMMARY

Introduction Diabetes mellitus patients are a vulnerable group of people who are prone to getting infected with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The virus has a high binding affinity to angiotensin-converting enzyme 2 receptor, which allows efficient host cell entering, prolonged virus retention, and a possibility of insulin resistance and ketoacidosis development.

Case outline We describe a case of a 20-year-old patient with a past medical history of type 1 diabetes mellitus who presented with bilateral COVID-19 pneumonia. Initially, treatment with polyvitamin therapy, corticosteroids, tocilizumab, and convalescent plasma did not improve the patient's condition, but might have led to the worsening of the underlying disease, high blood glucose level, and ketoacidosis. Patient developed a rapid progression of the disease and severe pneumonia that required intubation and mechanical ventilation. Intravenous immunoglobulin (IVIg) was administrated in order to suppress a hyperactive immune response through its immunomodulatory effect. Forty-eight hours later, respiratory gas exchange was improved, almost complete regression of changes in the lungs was seen, normalization of metabolic and gas exchange parameters was detected. After 14 days of hospitalization, the patient was discharged in good general condition.

Conclusion COVID-19 complicated by diabetes mellitus leads to a poor outcome of the disease, but antiviral and anti-inflammatory activity of IVIg suggests that it may be a useful therapeutic agent in cases of COVID-19. In the presented case, the application of IVIg led to a rapid improvement in the patient's condition.

Keywords: COVID-19; diabetic ketoacidosis; immunoglobulin; pneumonia

INTRODUCTION

Corona virus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), a virus with strong transmissibility that has rapidly evolved into a pandemic [1]. The disease spreads rapidly and has a high mortality rate. About 14% of patients require hospitalization and oxygen therapy and 5% of patients require admission to the intensive care unit (ICU) [2]. SARS-CoV-2 activates both innate and acquired immune response. Infected endothelial cells, mononuclear macrophages, neutrophils and maturated dendritic cells (innate immunity) produce pro-inflammatory mediators, such as interferon, cytokines [tumor necrosis factor α, interleukin (IL)-6] and chemokines, which recruit other components of the immune system [3]. The subsequent acquired immune responses including T lymphocytes (CD4+ and CD8+ T cells) and B lymphocytes play an important role in the defense. CD4+ T cells stimulate B cells to produce virus-specific antibodies, while CD8+ T cells are able to directly kill virus-infected cells. However, SARS-CoV-2 can induce excessive and prolonged inflammatory responses, known as the cytokine storm. Excessive neutrophil extracellular traps production, by neutrophils, can enhance tissue damage and may contribute to the cytokine storm, while activated B cells may contribute by production of IL-6. In patients with severe COVID-19, the cytokine storm causes acute respiratory distress syndrome or multiple-organ dysfunction [3].

Since SARS-CoV-2 affects the host immune system, there is a possibility of introducing intravenous immunoglobulin (IVIg) administration in the therapy of COVID-19 with the aim of improving immune response of the host [4].

CASE REPORT

A 20-year-old female, body mass index 22 kg/m^2, was admitted to the temporary COVID hospital of Zvezdara University Medical Center with positive real-time reverse transcription polymerase chain reaction (rRT-PCR) assay for SARS-CoV-2 and with a radiographic diagnosis of bilateral pneumonia (Figure 1). Six days prior to presentation, the patient complained of fatigue, tiredness and dry cough. On admission, the patient presented conscious, adynamic, pale skin and visible mucous membranes, highly febrile with a pronounced dry cough and breath that smelled like acetone. She had a history of

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Correspondence to:
Maja STOJANOVIĆ
Zvezdara University Medical Center
Department of Anesthesiology and Intensive Care
Dimitrija Tucovića 161
11000 Belgrade, Serbia
majastojanovic05@gmail.com

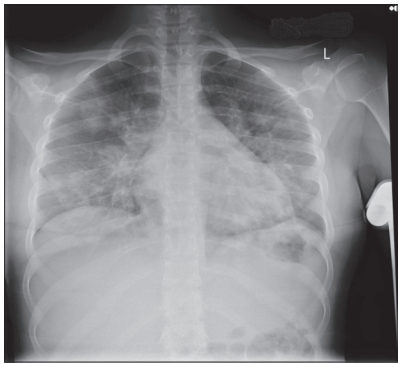

Figure 1. Chest radiograph at admission to the hospital

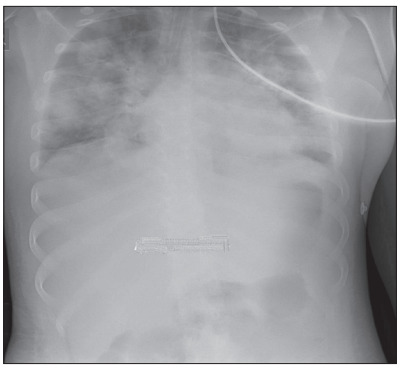

Figure 2. Chest radiograph at admission to the intensive care unit (11 days from the onset of the disease)

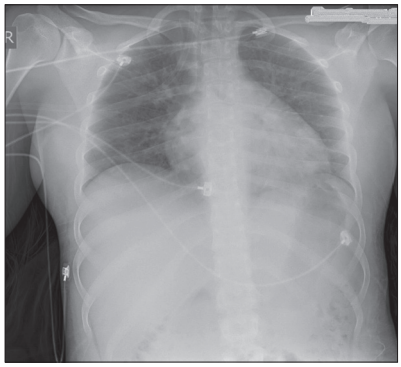

Figure 3. Chest radiograph 48 hours after immunoglobulin administration

type 1 diabetes mellitus diagnosed at the age of 13 and she was being treated with insulin. Hematologic, biochemistry and acid-base analysis before and after the treatments in ICU are presented in Tables 1 and 2.

Table 1. Hematologic and biochemistry analysis before and after the treatments

Parameters	On admission to the hospital	Before immunoglobulin administration	Forty-eight hours after immunoglobulin administration	At ICU discharge	At hospital discharge
WBC (10^9/L)	11	10.3	10.2	16.6	12.3
PLT count (10^9/L)	374	447	546	482	389
Neutrophil count (%)	76.7	66.8	68.9	77.7	67.3
Lymphocyt count (%)	11.7	19.7	18.2	11.1	23.7
CRP (mg/L)	96.1	163.1	81.5	24.5	4.2
Feritin (ng/ml)	427	402	265	184	156
LDH (U/L)	702	739	624	613	689
K^+ (mmol/L)	4.24	1.6	2.7	3.7	4
Glucose (mmol/L)	14	19.5	8.6	7.5	6.7

WBC – white blood cells; PLT – platelets; CRP – C-reactive protein; LDH – lactate dehydrogenase; K+ – potassium, ICU – intensive care unit

Table 2. Acid-base analysis before and after the treatments

Parameters	On admission to the hospital	Before immunoglobulin administration	Forty-eight hours after immunoglobulin administration	At ICU discharge	At hospital discharge
pH	7	7.13	7.52	7.54	7.34
pO_2 (mmHg)	120.6	74.7	96	88.5	110
pCO_2 (mmHg)	9.9	14.1	27.2	23.1	34
spO_2 (%)	90	90	97	97	97
HCO_3^- (mmol/L)	2.8	8.5	15.6	18.7	19.2
BE (mmol/L)	-3.5	-22.2	-12.7	-4.2	2.3
Lactate (mmol/L)	2.8	3.27	1.1	1.2	1.1

ICU – intensive care unit; pO_2 – oxygen partial pressure; pCO_2 – carbon dioxide partial pressure; spO_2 – oxygen saturation in the blood; HCO_3^- – bicarbonates; BE – basic excess

On the first day of hospitalization, the treatment was provided with vitamins (alphacalcidiol tablets 1 × 2 mcg, vitamin C 1 × 1 g), anticoagulant therapy (nadroparin 4000 U s.c.), corticosteroid therapy (prednisone tablets 0.5 mg/kg twice daily), proton pump inhibitors for gastric protection. Diabetic ketoacidosis (DKA) management was started (insulin and crystalloid fluids infusion, bicarbonate compensation) and antibiotic for bacterial super infection prevention was also performed (third-generation cephalosporin, ceftriaxone 2 g). Twenty-four hours after admission, somnolence, high fever (39°C), fatigue, hypotension (90/50 mmHg), tachycardia (hearth rate above 120 beats/min), tachypnea (respiratory rate 35 breaths/min), shortness of breath, blood oxygen saturation (spO_2) of 90% and normal glucose level (6.6 mmol/L) were observed. Oxygen supplementation was provided by a mask and oxygen flow of 5 l/min and spO_2 increased up to 97%. The next day blood analysis showed IL-6 value of 44.6 pg/ml, immunosuppressant (tocilizumab 600 mg) and convalescent plasma were administered. This did not result in clinical improvement – after 48 hours she became extremely dyspneic, tachypneic, tachycardic, hypotensive, blood tests revealed high glucose level (19.5 mmol/L) and ketoacidosis, while chest radiography showed progression of pneumonia (Figure 2). Due to the worsening of the general condition, the patient was transferred from the ward to the ICU. Since the blood gas exchange worsened, invasive mechanical ventilation with lung protection strategies was initiated immediately upon admission to the ICU (11 days from the onset of the disease). Due to the rapid disease progression complicated with ketoacidosis and unsatisfactory response to the applied therapy, it was decided to continue with the local therapeutical protocol and apply IVIg (10 g once). Forty-eight hours later, chest radiography showed almost complete regression of the changes in the lungs (Figure 3), inflammatory markers were decreased, metabolic disorder corrected, blood gas exchange was normalized and the patient was extubated. After 14 days in the hospital, the patient was discharged home without oxygen supplementation, afebrile, eupneic, with normal system function, normal laboratory and metabolic findings, and with a negative PCR test.

This case report was approved by the institutional ethics committee, and written consent was obtained from the

patient for the publication of this report and any accompanying images.

DISCUSSION

COVID-19 is a disease that leads to a high mortality rate. Local guidelines on the treatment of patients with COVID-19 exist, but mainly include symptomatic treatment and supportive care. Clinical manifestations of COVID-19 are non-specific, the disease can be asymptomatic or it can present with symptoms such as fever, dry cough, myalgia, fatigue, headache, diarrhea, and many others [5]. COVID-19 is classified as mild, moderate, or severe disease. However, COVID-19 can sometimes have a fulminant evolution rapidly leading to death [6]. It is assumed that a history of the underlying diseases can be associated with the development of severe illness [7].

Prevalence of diabetes in COVID-19 patients is high and is associated with the increased risk of complications and poor outcome. The majority of COVID-19 patients are patients with type 2 diabetes mellitus (9.7–10.9%) [8]. DKA prevalence before the pandemic was 0.72% and during the pandemic it increased up to 3.14%, while DKA mortality rate during the pandemic increased from 18% up to 46.3% [9]. Diabetes is causally associated with upregulated angiotensin-converting enzyme 2 receptor (ACE_2) expressions in the lungs, which may increase susceptibility to the SARS-CoV-2. The virus has a high binding affinity to the ACE_2 receptor [10], which allows efficient host cell entering and prolonged virus retention. ACE_2 is widely expressed in multiple organs, including pancreas, so the virus infection can lead to the pancreatic damage resulting in the development of insulin resistance and ketoacidosis. Elevated glucose levels directly increase SARS-CoV-2 replication. In this way hyperglycemia might support viral proliferation [10].

In addition, the virus directly damages the cells, especially T cell function, which can be reduced. CD4+ T lymphocytes are quickly activated into T helper-1 cells, leading to the high secretion of inflammatory cytokines (IL-6) [11]. IL-6 is an important cytokine of hyperinflammation in COVID-19, which is already increased in patients with underlying type 1 diabetes mellitus and triggers ketogenesis [11].

This case report shows the application of a local therapeutical protocol for COVID-19 and the management of DKA at the same time. Since the patient had rapid disease progression and all therapeutical options were exhausted, IVIg was used as a potent and safe immune modulator [12]. IVIg is a therapeutical product of normal human polyclonal IgG obtained from the pooled plasma of a large number of healthy donors. IVIg product used in this case (Ig VENA, Kedrion S.p.A., Barga, Italy) contains human normal immunoglobulin, mainly IgG (at least 95%). Initially, IVIg was used as a replacement therapy in patients with immunodeficiency disease in order to prevent infections by pathogen neutralization [13]. Today, it's widely used for a number of autoimmune and inflammatory diseases, including viral pneumonias. Several published studies showed potential benefits of IVIg therapy in SARS, MERS, influenza, and RSV infections and that's why it has been considered for COVID-19. These viral infections are associated with an excessive and uncontrolled complement activation, which contributes to tissue damage and hyperinflammation. IVIg treatment of this infections may reduce complement activation, bind and block C5a and C3a, leading to the decrease of hyperinflammation [14]. IVIg has numerous modes of action, such as inhibition of T-cell activation and proliferation, down-regulation of antibodies' production by B cells, interruption of complement activation cascade, and cytokine modulation (neutralization of inflammatory cytokines, chemokines and complement fragments by endogenous antigen-specific IgG which are present in IVIg), inhibition of neutrophil recruitment and activation and limitation of the differentiation of macrophages (these effects may be induced by blocking the activation of Fcγ receptors on innate immune effector cells), and many more [3, 14].

To date, the possitive effects of IVIg therapy in severe COVID-19 patients have been described in several case reports and studies, where IVIg therapy differs in doses, lenght of administration, and comorbidites. Currently, there is no consensus on IVIg treatment for COVID-19. A big multicentre retrospective study showed that 28-day mortality was not different between the group of COVID-19 patients treated with IVIg and non-IVIg group, so further investigations of efficacy of IVIg administration are needed [15]. Studies also showed that the administration of a high dose of IVIg within first 48 h promotes benefits such as the reduction of the use of mechanical ventilation and shorter ICU length of stay and the reduction of the mortality rate [16]. Several case reports of multisystem inflammatory syndrome in adults that presents 2–6 weeks after COVID-19 infection have been published thus far. In these cases, the combined administration of a high dose of corticosteroids and IVIg had better results compared to corticosteroid or IVIg monotherapy [17]. In contrast to previous studies, in the present case, high doses of corticosteroids and lower doses of IVIg were administered during the period when mechanical ventilation was applied, which led to an improvement in the condition. Therefore, further studies are needed to determine the dose and the timing of IVIg administration, as well as at what stage of the disease should the therapy be applied.

This case report showed that initially applied therapy did not result in clinical improvement; the disease had rapid progression complicated by an underlying condition and an inadequate immune response, which led to the decision to apply the last step of the protocol algorithm. Shortly after the IVIg administration, the patient improved clinically, a significant decrease of white blood cells, ferritin and lactate dehydrogenase levels was seen, gas exchange improved and chest radiography showed significant improvement as well. The patient was extubated and after 14 days of hospitalization she was discharged in stable condition.

The main limitation of this case report is that the patient received tocilizumab, convalescent plasma, and higher doses of corticosteroids prior to IVIg. Some of these

drugs may have influenced the course of the viral disease and enhanced the efficacy of IVIg. The lack of efficacy of convalescent plasma could have resulted from insufficient titers of neutralizing antibodies or the timing of administration, while the anti-inflammatory and immunemodulatory effects on the various immune cells of IVIg may account for its clinical benefits.

Considering the immunomodulatory effects of IVIg its application has a potential role in the treatment of the severe COVID-19. Intravenous immunoglobulins are in use for severe and critically ill COVID-19 patients, but available data is still limited and without clinical confirmation. Therefore, additional detailed well-designed studies of IVIg administration in severe COVID-19 patients are needed.

Conflict of interest: None declared.

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Ефикасност интравенских имуноглобулина у лечењу болесника са ковидом 19

Маја Стојановић[1,2], Милан Марковић[2], Дубравка Ђиновић[2], Слободан Поповић[2], Јела Боровинић[3]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетски медицински центар „Звездара", Служба за анестезију, реанимацију и интензивно лечење, Београд, Србија;
[3]Универзитетски медицински центар „Звездара", Служба за снабдевање крвљу и крвним продуктима, Београд, Србија

САЖЕТАК

Увод Оболели од шећерне болести представљају осетљиву групу људи склону инфекцији коронавирусом 2, који изазива тешки акутни респираторни синдром (*SARS-CoV*-2). Вирус има већи афинитет везивања за рецепторе ензима за конверзију ангиотензина, што омогућава ефикасан улазак вируса у ћелију, дуже задржавање вируса и могућност настанка инсулинске резистенције и развој кетоацидозе.

Приказ болесника Приказан је случај особе старости 20 година која болује од шећерне болести типа I са билатералном ковид 19 пнеумонијом. Примењена поливитаминска, кортикостероидна терапија, тоцилизумаб и плазма реконвалесцената нису довели до побољшања стања, а постоји могућност да су довели до погоршања основне болести, појаве високе вредности шећера у крви и развоја кетоацидозе. Због рапидног напредовања болести и погоршања упале плућа болесница је интубирана и механички вентилирана. У терапију су уведени имуноглобулини (*IVIg*) због своје способности модулације имунитета. Након 48 сати долази до побољшања гасне размене, скоро потпуне регресије промена на плућима, нормализације метаболичких и параметара гасне размене. Болесница је након 14 дана отпуштена на кућно лечење у добром општем стању.

Закључак Ковид 19 компликован шећерном болешћу доводи до лошег исхода болести, али антивирусна и противупална активност *IVIg* наводи на размишљање да може представљати корисно терапијско средство и у случају ковида 19. Код приказаног случаја примена *IVIg* је врло брзо довела до побољшања стања болесника.

Кључне речи: ковид 19; дијабетесна кетоацидоза; имуноглобулини; запаљење плућа

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Decoronation – a treatment option of an ankylosed permanent tooth in children and adolescents

Boris Gašpirc[1], Tina Leban[2], Zoran Mandinić[3], Alenka Pavlič[2]

[1]University of Ljubljana, Faculty of Medicine, Department of Oral Medicine and Periodontology, Ljubljana, Slovenia;
[2]University of Ljubljana, Faculty of Medicine, Department of Pediatric and Preventive Dentistry, Ljubljana Slovenia;
[3]University of Belgrade, School of Dental Medicine, Clinic for Pediatric and Preventive Dentistry, Belgrade, Serbia

SUMMARY
Introduction In children and growing adolescents, ankylotic resorption (i.e., progressive replacement resorption) of a permanent tooth is a serious complication. An ankylosed tooth root is continuously resorbed and replaced with bone; normal growth of alveolar bone is disturbed and infraposition of the dental crown progresses. This article aims to present decoronation as a very good treatment option for permanent incisors diagnosed with progressive replacement resorption in children and adolescents.
Case outline A 9.5-year-old boy was referred with non-vital both upper central permanent incisors due to dental trauma. In the left one, which had been re-implanted 90 minutes after avulsion, progression of clinical and radiographic pathological signs of ankylotic resorption was observed over the months. To prevent the local arrest of alveolar ridge growth and tilting of adjacent teeth, we decoronated the ankylosed tooth. For aesthetic and functional rehabilitation adhesive bonding of his dental crown was performed.
Conclusion In growing individuals with progressive replacement resorption, a dentist should be aware of decoronation as an effective treatment option with a predictable outcome.
Keywords: decoronation; progressive replacement resorption; ankylosis; bone preservation; infraposition

INTRODUCTION

Severe dental traumas often result in a variety of complications; one of them is ankylotic resorption (also known as progressive replacement root resorption or dentoalveolar ankylosis). With ankylotic resorption, the tooth root is gradually resorbed, and replaced by bone. This process can progress over many years. The rate of resorption varies between individuals and depends on age, basal metabolic rate, extra-alveolar time of the tooth, root surface treatment before replantation, amount of root dentin at the time of the trauma, the severity of the trauma, and the extent of periodontal ligament necrosis [1].

Commonly, ankylotic resorption may develop in teeth reimplanted after complete separation of its alveolus (i.e., tooth avulsion). Most frequently, avulsion occurs in children aged between seven and 10 [2]. Avulsion of a permanent tooth is an emergency condition that requires immediate action [3]. From the moment the tooth is avulsed from the alveolar socket, time is the most important factor. In addition to the length of extra-alveolar time, the healing process of the reimplanted tooth is influenced by various factors, including the age of the patient, handling of the avulsed tooth before replantation [4]. As the time between avulsion to reimplantation lengthens, the likelihood of a favorable outcome decreases rapidly. In non-physiological conditions, cementoblasts die on the root surface [5]. After tooth reimplantation, a severely damaged periodontal ligament prevents its regeneration. In such damaged periodontium, gradual development of ankylotic resorption is always expected [2]. The long-term prognosis of so affected tooth is poor.

This report aims to present a clinical case of a child who underwent decoronation treatment needed due to progressive replacement resorption of his permanent incisor.

CASE OUTLINE

A 9.5-year-old boy was referred to the University Medical Centre of Ljubljana, Division of Stomatology due to complications related to dental trauma. Both upper central permanent incisors suffered an injury when he fell off his bicycle a month and a half ago. The left incisor was knocked out, and a tooth crown of the right incisor was fractured and with the exposed pulp. The avulsed tooth was reimplanted after 90 minutes.

A clinical examination a month and a half after the injury revealed a negative response on cold and electrical testing of both traumatized incisors. The right one showed also some

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Correspondence to:
Alenka PAVLIČ
Faculty of Medicine
Department of Pediatric and Preventive Dentistry
Hrvatski trg 6
1000 Ljubljana
Slovenia
alenka.pavlic@mf.uni-lj.si

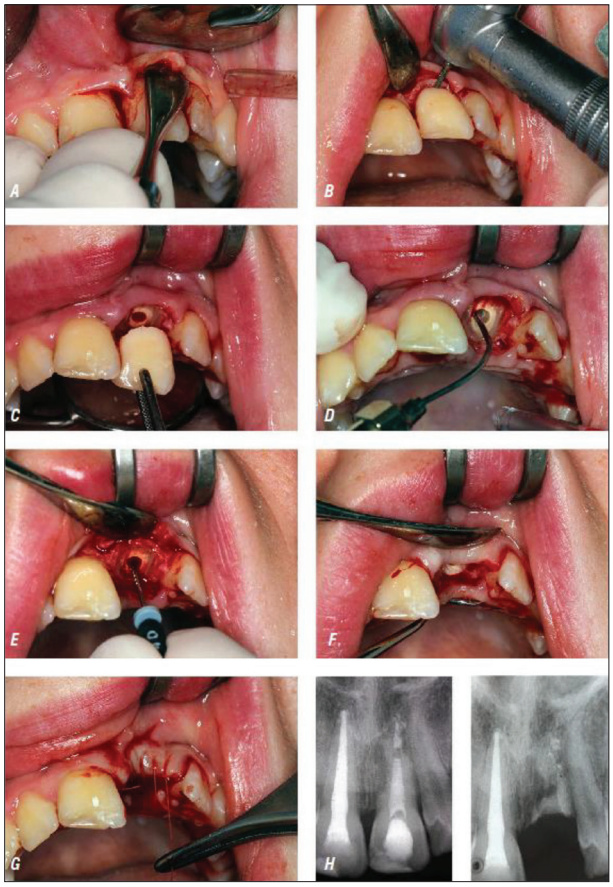

Figure 1. Decoronation of ankylosed and infrapositioned upper left central incisor in a 9.5-year-old boy; A – following administration of local anesthesia, a full-thickness buccal mucoperiostal flap is elevated; the palatal tissue is left intact; B – The crown of the ankylozed incisor is cut with a diamond bur 1–2 mm below the alveolar bone crest under continuous saline irrigation; C – the dental crown is removed; D – from the root canal, calcium hydroxide is washed out (Calxyl, O OCO Präparate GmbH, Dirmstein, Germany); E – the root canal is endodontically instrumented and copiously rinsed with saline; F – As bleeding filled the empty root canal; G – the mucoperiosteal flap is repositioned and sutured; H – on x-rays taken two months after the dental trauma (the incisor was reimplanted 1.5 hours after avulzion); I – after decoronation

tenderness on palpation and was pathologically mobile. X-ray taken at this visit displayed inflammatory and replacement resorption of the right and left incisor, respectively. Therefore, we started root canal treatment of both non-vital teeth.

Seven weeks later, a root canal of the right incisor was tightly sealed with guttapercha and root canal sealer AH Plus (Dentsply Sirona, York, PE, USA). In the root canal of the left incisor, calcium hydroxide (Calxyl, OCO Präparate, Dirmstein, Deutschland) was replaced periodically, with the tight placement of temporary coronary filling after each section.

Six months after dental trauma, minor infraoccusion was already observed. High metal percussion sound and decreased mobility of the tooth were also noted. Over the months, we observed progression of clinical (e.g., infraocclusion) and radiographic pathological signs (disappearance of the width of the periodontal ligament, progression of the root resorption, and its replacement with bone). Two years after the occurrence of dental trauma, decoronation of the ankylosed tooth crown was performed to prevent

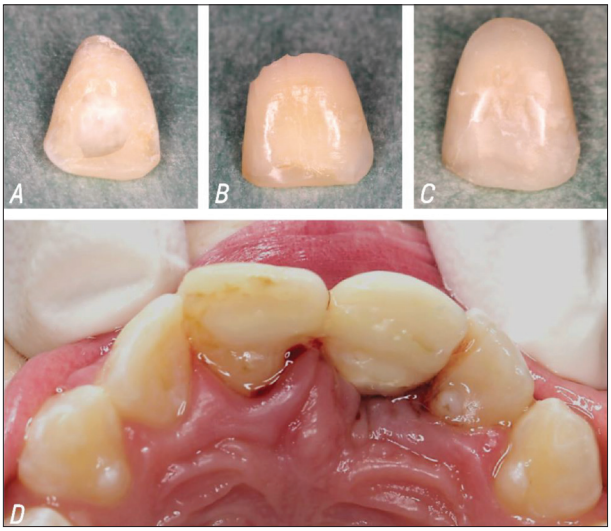

Figure 2. After decoronation; A – the cut tooth crown is thoroughly cleaned, the pulp chamber filled in layers with composite; B and C – appropriately shaped; D – the palatal surfaces of the crown and both adjacent teeth are then etched with 37% phosphoric acid, washed, and dried; this is followed by application and polymerization of an adhesive, adjustment of resin-soaked polyethylene fibers, and application and polymerization of low-viscosity composite; the result is the immediate aesthetic and functional outcomes, with which the patient is also satisfied

the local arrest of alveolar ridge growth and tilting of adjacent teeth (Figure 1). Immediately afterward, the boy was aesthetically and functionally rehabilitated with his dental crown (Figure 2).

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

Normally during the growth of children, the forces of periodontal and gingival fibers allow bone apposition on top of the interdental septum [6]. In the area of an ankylosed tooth, with partly or completely resorbed periodontal fibers, the marginal bone development terminates and the tooth eruption arrests. Due to cessation of the formation of the alveolar bone formation, infraposition of an ankylosed tooth develops, which may result in an unaesthetic dento-gingival complex and/or a complication in future prosthetic rehabilitation [4]. Furthermore, the still present interdental fibers between the ankylosed tooth and the adjacent ones cause tipping of the adjacent teeth as they continue to erupt. In the growing patient, progressive replacement resorption not only leads to the inevitable loss of the traumatized tooth but also affects the alveolar bone formation and the eruption of adjacent teeth [7, 8].

A slowly progressive resorption process of the ankylotic root allows the dentist to decide on the appropriate timing for therapy; the prosthetic rehabilitation can be a postponement to an appropriate time. The ankylotic tooth should be monitored regularly, without any intervention, unless tilting of adjacent teeth or moderate infraposition

develops. The progression of infraposition depends on the age, gender, and skeletal growth pattern of the patient [8]. Cases with severe infraposition of ankylosed teeth indicate serious aesthetic and functional disturbances. To avoid such complications, one or more appropriate treatment procedures should be performed in a timely manner.

Unlike in an adult patient, in growing individuals' therapy with a dental implant is not recommended. Osseointegrated implants lack the compensatory growth mechanism of the natural teeth; in young patients' implants behave similarly to ankylosed teeth. It is not until skeletal growth and development are completed that the placement of dental implants can be considered [4]. Immediate extraction upon diagnosis of irreversible ankylosis is also not routinely recommended. Extraction of the ankylosed tooth often leads to major bone loss, compromising the subsequent implantation and prosthetic solutions [5].

Decision on the selected treatment of ankylosed permanent teeth should include additional considerations, such as diagnosis of adjacent teeth, type of occlusion, age of the patient, and the root development of potential donor teeth if autotransplantation is planned [9]. In some cases, orthodontic space closure provides esthetic solution and rehabilitation of the alveolar bone ridge. Composite built-up of a crown improve the appearance of an orthodontontically-translocated tooth. Autotransplantation of a premolar is also an alternative treatment option in a child. Viable periodontal ligament of the transplanted tooth will induce continuous development of bone formation and if necessary, enable orthodontic treatment [10]. The premolar crown builds up with composite and the gradual grinding of the tip of the palatal cusp will provide the appropriate esthetics.

In the majority of pediatric cases with progressive replacement resorbtion, decoronation is a highly recommended treatment option with a predictable success. Yet, many clinicians are unaware of this treatment option [5]. Decoronisation can be performed in a patient in whom an implant or a dental bridge replacement is planned in the future, and has no medical, surgical or orthodontic contraindications [4]. Following decoronation, the patient should be provided with optimal interim dental rehabilitation. This decision on the selected rehabilitation may be influenced by the occurrence of dental caries, the eruption of adjacent teeth, occlusion, presence or absence of tooth buds, and the future planned dental treatment. If subsequent implant insertion is foreseen, it is especially advisable to keep adjacent teeth intact.

With decoronation and removal of the filling material from the root canal, the volume of the alveolar bone ridge is preserved. If the entire crown (i.e., enamel) and the root-canal filling have been completely removed, root resorption is predictable. Within a few years, no remnants of decoronated root can be observed on X-rays [5]. Given subsequent implant placement, decoronation facilitate future rehabilitation with minimal or no ridge augmentation procedures.

A dentist should be familiar with the treatment options for ankylosed permanent teeth. In growing individuals, decoronation is a treatment option that allows proper eruption of adjacent teeth and preservation of alveolar bone, provides good immediate rehabilitation with quality functional and dental aesthetic appearance, and facilitates future planned prosthetic and/or implant rehabilitation.

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Декоронизација – могућност лечења анкилозираног сталног зуба код деце и адолесцената

Борис Гашпирц[1], Тина Лебан[2], Зоран Мандинић[3], Аленка Павлич[2]

[1]Универзитет у Љубљани, Медицински факултет, Одељење оралне медицине и периодонтологија, Љубљана, Словенија;
[2]Универзитет у Љубљани, Медицински факултет, Одељење педијатријске и превентивне стоматологије, Љубљана, Словенија;
[3]Универзитет у Београду, Стоматолошки факултет, Клиника за дечју и превентивну стоматологију, Београд, Србија

САЖЕТАК

Увод Код деце и адолесцената у развоју анкилоза (тзв. прогресивна заменска ресорпција) сталног зуба представља озбиљну компликацију. Анкилозирајући корен зуба континуирано се ресорбује и замењује га кост, нормалан раст алвеоларне кости бива поремећен, што доводи до инфрапозиције крунице зуба.

Овај чланак представља декоронизацију као одличну могућност лечења сталних секутића код којих је дијагностикована прогресивна заменска ресорпција код деце и адолесцената.

Приказ болесника Дечак од девет и по година долази са оба авитална горња централна стална секутића због трауме зуба. Код левог, који је био реимплантиран 90 минута након авулзије, током месеци је примећено напредовање клиничких и радиографских патолошких знакова анкилотичке ресорпције. Да бисмо спречили локално заустављање раста алвеоларног гребена и нагињање суседних зуба, декоронизирали смо анкилозирани зуб. За естетску и функционалну рехабилитацију извршено је лепљење сопствене крунице зуба.

Закључак Стоматолог треба да буде упознат са декоронизацијом као ефикасном методом лечења са предвидљивим исходом код деце и адолесцената са прогресивном заменском ресорпцијом корена зуба.

Кључне речи: декоронизација; прогресивна заменска ресорпција; анкилоза; очување костију; инфрапозиција

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Ectopic thyroid nodes in the mediastinum – report of two cases

Aleksandra Đurić-Stefanović[1,2], Dušan Šaponjski[1], Katarina Stošić[1], Stefan Milošević[1]

[1]University Clinical Center of Serbia, Center of Radiology and Magnetic Resonance, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Ectopic thyroid is a rare anomaly characterized by presence of thyroid tissue outside its normal location, which could be the consequence of developmental abnormality, sequestration of thyroid nodes from nodal thyroid goiter or mechanical implantation of thyroid tissue after resection or trauma. Ectopic thyroid is commonly incidentally detected and causes differential diagnostic dilemma towards the neck and mediastinal tumors. The object of this report was to present two types of ectopic thyroid nodes located in the upper mediastinum, incidentally discovered by computed tomography (CT).

Outline of cases A hyperdense nodular lesion was found in the anterior upper mediastinum in a 42-year-old woman with adenocarcinoma of the esophagogastric junction in whom CT was performed due to staging purposes. Metastatic left supraclavicular lymph node was considered in the differential diagnosis. However, as the node was located in front of the neck fascia and just below the thyroid gland and showed similar density to thyroid tissue, the diagnosis of accessory thyroid gland was made, which was later confirmed by multiple repeated CT scans during the two-year follow-up period.

In a 52-year-old woman presenting with intermittent chest pain and cough, contrast-enhanced CT scan revealed nodal thyroid goiter and three nodes of similar CT texture, located in the upper mediastinum, below the thyroid gland. Accordingly, the diagnosis of parasitic mediastinal goiter thyroid nodes was made.

Conclusion Ectopic thyroid nodes are presented by CT as well-circumscribed nodes of the same density as the thyroid gland, typically located anteriorly in the upper mediastinum.

Keywords: thyroid gland; computed tomography; ectopic thyroid nodes; accessory thyroid gland

INTRODUCTION

Ectopic thyroid is a rare developmental disorder, characterized by the presence of thyroid tissue outside its normal location. Most commonly it is located along the way of descent of the thyroid gland, along the thyroglossal duct, from the base of the tongue to the infrahyoid part of the neck [1, 2]. However, thyroid tissue can rarely be found at certain distant sites [1–11]. Patients are mostly asymptomatic and ectopic thyroid is usually detected incidentally. As an increasing number of patients are undergoing ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) examinations, these anomalies are being seen more frequently [12, 13]. This can cause serious diagnostic dilemma especially towards the lymph node metastasis from occult thyroid carcinoma or other malignant tumors [12, 13]. We report two cases of ectopic thyroid nodes located in the upper mediastinum, which were incidentally discovered on CT exams.

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Correspondence to:
Aleksandra ĐURIC-STEFANOVIĆ
Department of Digestive Radiology
(First Surgery University Clinic)
Center of Radiology and MR
Koste Todorovića 6
11000 Beograd, Serbia
aleksandra.djuricstefanovic@gmail.com

CASE REPORTS

Case 1

The first patient was a 42-year-old woman with the adenocarcinoma of the esophagogastric junction, which was diagnosed by endoscopy. Preoperative contrast-enhanced CT scan of the neck, thorax, and abdomen was performed due to staging purposes and an oval well-circumscribed soft tissue mass 2 cm in diameter was detected, located at the upper mediastinum just below the left lobe of the thyroid gland and in front of the trachea. The lesion was hyperdense in comparison to neighboring skeletal muscles in both noncontrast and contrast-enhanced phase of CT, and isodense to the tissue of the thyroid gland (Figure 1a–c). It was not accessible for US visualization due to its deep location in the upper mediastinum. The patient underwent laparoscopic surgery for esophagogastric carcinoma. Four months later, the first postoperative CT scan was done and the lesion was same in size and shape. In the next two-year follow-up period, several additional CT examinations revealed that the lesion remained unchanged (Figure 1d). Accordingly, the diagnosis of accessory thyroid gland was clinically confirmed.

Case 2

The second patient was a 52-year-old woman presenting with intermittent chest pain and cough. She had a history of prolonged cough with expectoration of blood-stained mucus one year before when she underwent a CT

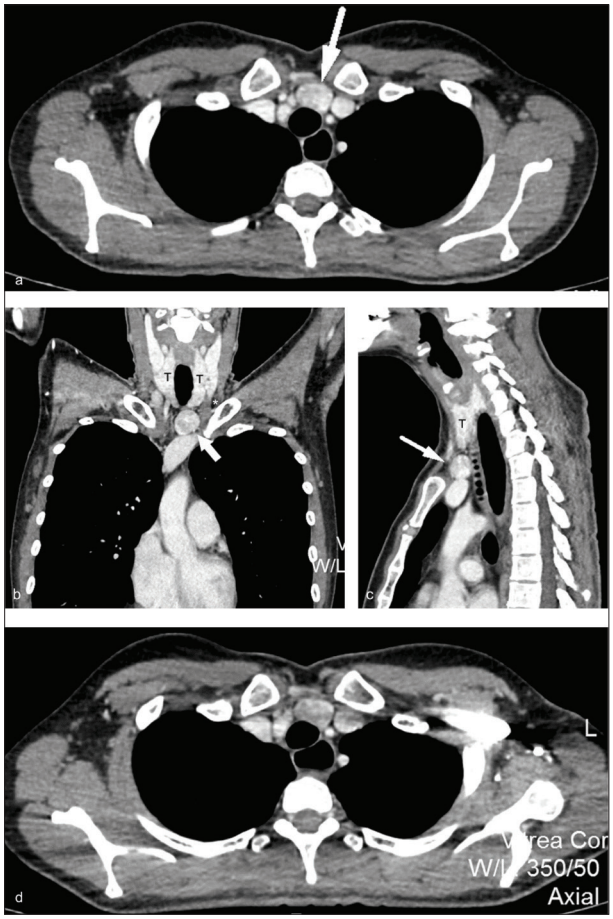

Figure 1. Ectopic thyroid node (arrow) on the axial section (a), coronal plane (T – thyroid gland, * – supraclavicular fossa) (b), sagittal plane (c), and follow-up computed tomography after two years (d)

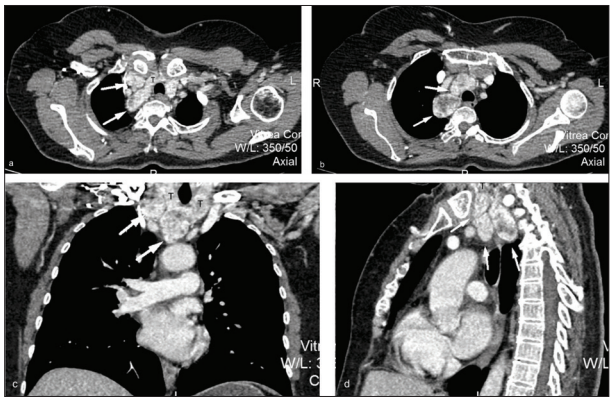

Figure 2. Three parasitic thyroid nodes (arrows) in the upper mediastinum below the nodular thyroid goiter (T) on the axial (a, b), coronal (c) and sagittal (d) sections of contrast-enhanced computed tomography

examination and right-sided mediastinal paratracheal lymphadenopathy was described by the radiologist. In actual contrast-enhanced CT scan, three well-circumscribed soft-tissue lesions of 3 cm, 4 cm, and 3 cm in diameter were detected in the upper mediastinum, below the thyroid gland and beside the right wall of the trachea (Figure 2a–d). The thyroid gland was enlarged with the hypodense node in the isthmus, which suggested the diagnosis of nodal thyroid goiter. Mediastinal nodes showed the same CT texture as the node in the isthmus of the thyroid gland. Laboratory findings revealed euthyroid hormonal state. To exclude metastatic thyroid malignancy, the patient was referred to scintigraphy. Scintigraphy with iodine-123 showed hyper uptake of radiotracer in the right lobe and isthmus of thyroid gland and no any uptake in the mediastinum. Accordingly, the diagnosis was nodular thyroid goiter with parasitic mediastinal goiter thyroid nodes. Surgical treatment (partial thyroidectomy and removing the parasitic mediastinal thyroid nodes) was planned but the operation was postponed due to the COVID-19 pandemic situation.

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

In the oncologic patient with the esophagogastric junction carcinoma, our diagnosis based on the repeated CT examinations was an accessory thyroid node located in the upper mediastinum. Differential diagnosis that we considered in this patient after initial CT exam was metastatic supraclavicular lymphadenopathy. It is well known that gastric cancer tends to metastasize in the left supraclavicular lymph node, i.e., Virchow's node. However, a key factor which influenced our conclusion was the exact site of the lesion. Metastatic Virchow's node is located deeper and more laterally in the left supraclavicular space (Figure 1a), while ectopic thyroid tissue is always in front of the neck fascia and just below the thyroid gland as was in our patient [1, 2]. Most importantly, the node showed similar density to the thyroid gland [13]. Multiple repeated CT scans during the two-year follow-up period supported our diagnosis.

In the second patient with respiratory symptoms, the presence of enlarged isthmus of the thyroid, extended retrosternally together with the multiple nodes of the same CT appearance located just below the thyroid and laterally in the mediastinum, suggested the diagnosis of parasitic goiter thyroid nodes associated with the nodal thyroid goiter [14].

Ectopic thyroid is a rare anomaly diagnosed in approximately 1 in 100,000–300,000 people, but more frequently found on autopsies, with higher prevalence in females [2]. Possible reasons of thyroid tissue being outside its normal location are developmental abnormality, sequestration of thyroid nodules from a multinodular thyroid goiter and mechanical implantation of thyroid tissue after resection or trauma of the thyroid gland [1, 2, 14, 15].

The most common cause of ectopic thyroid is embryological developmental abnormality [1, 2]. The thyroid gland is normally located in the anterior neck, just below the larynx and in front of the trachea (spanning from the second to the fourth tracheal ring). During development, the thyroid gland is formed from endodermal cells that

originate from the third branchial pouch in the floor of the primitive pharynx, at the base of the tongue (foramen cecum) [1, 2]. Throughout further development, the gland descends from the base of the tongue, reaching the midline of the neck to the hyoid bone, after which it loops inferiorly to the infrahyoid portion of the neck, inserting itself between the thyroid cartilage and thyroid membrane [1, 2]. During descend, there is a rare possibility that thyroid embryonic cells fail to migrate along their pathway, which forms the ectopic thyroid gland. The ectopic locations are usually from the foramen cecum at the base of the tongue to the anterior midline of the neck and all the way to the upper mediastinum, and the lingual thyroid is the most common location (found in 90% of all cases) [16]. Rarely, it can be found below the way of thyroid descent in the midline or laterally in the mediastinum like in cases which we presented or even below the diaphragm [3–11, 16, 17, 18]. Ectopic thyroid is often asymptomatic, but if there are symptoms, they would be a result of mass effect on adjacent structures, causing cough, dyspnea, or dysphagia [3, 16].

The thyroid gland, as well as the spleen, both being hypervascular organs, has a possibility of auto implantation of one or more focal deposits of splenic and thyroid tissue after surgery, known as splenosis and parasitic thyroid nodules, respectively [19]. A comparison can also be made between splenunculum and ectopic thyroid nodes, i.e., accessory spleen and accessory thyroid as these are small nodules of tissue, which are separated from the rest of the organ [19].

Radiological imaging modalities, such as US, CT, and MRI, have been deemed very useful for detection and evaluation of ectopic thyroid. Ectopic thyroid has approximately the same radiological characteristics on all imaging modalities as the orthotropic thyroid gland. It is usually oval and well-circumscribed. On US, the ectopic tissue of the thyroid gland is hyperechogenic. US as the most accessible and the safest radiological modality is mainly used for the detection of ectopic tissue in the neck, but is of limited diagnostic value in other locations [14]. The ectopic focuses of the thyroid gland are mostly incidentally detected on CT examinations, especially distant, extra cervical sites such as the abdomen or, as in our cases, the mediastinum. A non-contrast CT scan shows ectopic thyroid tissue as hyper dense compared to skeletal muscles, due to higher iodine concentration in the thyroid tissue [12, 13]. Contrast enhanced CT scan shows ectopic thyroid as homogeneously enhancing mass the same as thyroid gland [13]. MRI is also very useful in detecting ectopic thyroid, which is hyper intense in both T1w and in T2w sequences [13].

Scintigraphy, using Tc-99m, I-131, or I-123 could be a valuable diagnostic tool to detect ectopic thyroid tissue [3, 12]. However, the literature reveals that, as in our case, ectopic thyroid tissue does not have to show radionuclide uptake in the separated nodules [12].

Fine needle aspiration cytology is also a very useful diagnostic method in confirming the diagnosis of ectopic thyroid, with specificity of 95–97%, but only in cases where ectopic thyroid is suitable for biopsy [3]. However, in cases of mediastinal or other deep localizations, the ultimate diagnosis is most accurately made by histological analysis, after surgical removal of mass [14].

Differential diagnosis of ectopic thyroid depends on the location, but thyroid cancer metastases should always be excluded first, as they can manifest as ectopic thyroid tissue.

Since in both of our cases ectopic thyroid tissue was located in the upper mediastinum retrosternally, differential diagnosis primarily included metastatic lymph nodes from papillary thyroid carcinoma, followed by the germ cell tumors, neurogenic tumors, lymphomas, thymic and parathyroid tumors [13]. Germ cell tumors, of which teratoma is the most common one, consisting of different tissues, are mainly presented as large well-circumscribed heterogeneous mass, usually cystic (90% of all cases) of variable density [20]. In both our cases the mass was mainly hyperdense on CT exams, and had no cystic component. Neurogenic tumors are more common in the posterior mediastinum and are mostly hypodense on CT, compared to skeletal muscles [12]. Lymphoma usually consists of enlarged lymph nodes in several mediastinal lymph node groups. Thymic tumors – thymoma – are hypodense, with cystic component and calcification that can be seen in some patients [20]. Parathyroid tumors are relatively easy to differentiate from ectopic thyroid since they are located posteriorly to the thyroid gland and show reduced post-contrast enhancement compared to the normal thyroid gland in the arterial phase and greater washout than the thyroid tissue in the delayed phase [13].

The treatment of ectopic thyroid depends mainly on localization and local symptoms; however, the age and the overall condition of the patient should also be considered. In most cases, the patients are asymptomatic and no treatment is needed, only regular follow-up. Follow-up imaging is also recommended since ectopic thyroid has the same histological structure as normal thyroid and can be affected by the same pathological changes (Hashimoto thyroiditis, goiter, or carcinoma) [14, 21]. If the patient is symptomatic due to mass effect on the surrounding structures, surgery is the treatment of choice.

In summary, ectopic thyroid nodes are rare entities that mainly occur as a result of a developmental anomaly. Parasitic thyroid nodes are sequestrated from the multinodular thyroid goiter. They are most commonly present in the neck, but can be rarely found in the mediastinum, and then cause diagnostic dilemma towards a spectrum of mediastinal tumors. Patients are mostly asymptomatic and euthyroid, but symptoms related to node size and location may develop. CT scan, as a leading diagnostic tool, shows well-circumscribed nodes of the same density as the thyroid gland located anteriorly in the upper mediastinum. Even though this entity is a rare disorder, clinicians should take it into consideration in differential diagnosis to other mediastinal masses.

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Ектопични тиреоидни нодуси у медијастинуму – приказ два случаја

Александра Ђурић-Стефановић[1,2], Душан Шапоњски[1], Катарина Стошић[1], Стефан Милошевић[1]

[1]Универзитетски клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Ектопична штитна жлезда је ретка аномалија коју карактерише присуство ткива штитасте жлезде ван њеног нормалног положаја, што може да буде последица развојне аномалије, секвестрације тиреоидних нодуса код нодозне струме, или механичке имплантације ткива штитасте жлезде након њене ресекције или трауме. Обично се случајно открива и узрокује диференцијално-дијагностичку дилему према туморима врата и медијастинума. Предмет овог рада је приказ два типа ектопичних тиреоидних нодуса локализованих у горњем медијастинуму који су случајно откривени компјутеризованом томографијом (КТ).

Прикази болесника Код 42-годишње жене са аденокарциномом езофагогастричног споја, којој је урађен КТ преглед ради стадирања карцинома, нађена је хипердензна нодуларна лезија у предњем горњем медијастинуму. У диференцијалној дијагнози је разматран метастатски измењен леви супраклавикуларни лимфни нодус. Ипак, како је нодус био локализован испред вратне фасције и непосредно испод штитасте жлезде и био сличног дензитета као ткиво штитасте жлезде, постављена је дијагноза акцесорне штитасте жлезде, што је касније потврђено понављаним КТ прегледима током двогодишњег периода праћења.

Код 52-годишње жене са симптомима повременог бола у грудима и кашља, постконтрастним КТ прегледом откривени су нодална струма штитасте жлезде и три нодуса сличне КТ текстуре локализована у горњем медијастинуму, испод штитасте жлезде. Према томе, постављена је дијагноза медијастиналних тиреоидних нодуса секвестрираних од нодозне струме.

Закључак Ектопични тиреоидни нодуси се КТ прегледом приказују као јасно ограничени нодуси истог дензитета као штитаста жлезда, локализовани антериорно у горњем медијастинуму.

Кључне речи: штитаста жлезда; компјутеризована томографија; ектопични тиреоидни нодуси; акцесорна штитаста жлезда

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A rare case of spontaneous rupture of renal artery pseudoaneurysm in a previously hypertensive patient

Dejan Stevanović[1,2], Nebojša Mitrović[1,2], Damir Jašarović[1,2], Aleksandar Lazić[1,2], Branko Lukić[2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Zemun Clinical Hospital Center, Clinic for Surgery, Department of General Surgery, Belgrade, Serbia

SUMARRY

Introduction The renal artery and segmental renal artery pseudoaneurysm is a rare and usually asymptomatic vascular lesion which in most of the cases thrombose spontaneously, but at same time it can be a source of life-threatening hemorrhage and shock. Today, these pseudoaneurysms are discovered with increasing frequency due to unrelated abdominal imaging or on screening work-ups for hypertension, as well as widespread use of angiography. Typically, they are seen in patients after trauma, inflammation, or renal surgery or biopsy.

Case outline In our case, a 52-year-old male patient with no prior history of surgery, significant abdominal trauma and systemic disease, presented with left flank pain and signs of hypovolemic shock that manifested before the admission to the surgical emergency room. The CT scan promptly demonstrated rupture of a large retroperitoneal hematoma with massive intraperitoneal hemorrhage. The angiography confirmed the rupture of the renal artery pseudoaneurysm. The patient underwent urgent operation. A life-saving nephrectomy was performed while intraperitoneal hemorrhage and retroperitoneal hematoma was evacuated. Fourteen days after surgery the patient was discharged fully recovered, with normal diuresis and serum levels of creatinine and urea within referential values. During the period of hospitalization, he was diagnosed with and treated for hypertension.

Conclusion Rupture of pseudoaneurysms followed by hemorrhage into the intraperitoneal cavity and retroperitoneum is a life-threatening condition, as proven with this case, in which hypovolemic shock manifested itself before the admission. We would like to highlight the importance of high blood pressure control and the importance of regular check-ups.

Keywords: renal artery pseudoaneurysm; rupture; life-threatening procedure

INTRODUCTION

Aneurysmal vascular lesions represent anomalous dilatations of the blood vessel lumen. Following the pathological condition of the vessel wall, these lesions are classified into true aneurysms and pseudoaneurysms. A true aneurysm signifies a circumscribed dilatation of an artery with the preservation of all three wall layers – intima, media, and adventitia. In 90% of the cases, they are extraparenchymal. [1, 2] In contrast, a pseudoaneurysm arises from the disruption of the arterial wall continuity and represents a perfused hematoma contained solely by the adventitia and perivascular tissues. These tissues usually wield sufficient compressive force to decrease the bleeding from the site of the lesion, allowing reactive fibrosis to occur and encapsulate the hemorrhage [3–6]. It may involve both the extraparenchymal or the intraparenchymal renal artery, as well as its branches [7, 8].

While it is a rare and usually asymptomatic vascular lesion which in most of the cases thrombose spontaneously, renal artery pseudoaneurysm (RAP) can be a source of a life-threatening hemorrhage and shock [9, 10]. Spontaneous pseudoaneurysm of the segmental renal artery is also a rare entity. Today, these pseudoaneurysms are discovered with increasing frequency due to unrelated abdominal imaging or on screening work-ups for hypertension, as well as widespread use of angiography [11]. Typically, they are seen in patients after trauma, inflammation, or renal surgery or biopsy [12, 13].

Here, we report a rare case of rupture of a spontaneous pseudoaneurysm from a segmental renal artery branch, presenting itself with extensive intra- and retroperitoneal hemorrhage in a patient with previously uncontrolled high blood pressure.

CASE REPORT

A 52-year-old male patient was admitted to surgical emergency room of our institution in a serious condition, somnolent to soporous, hemodynamically unstable, with extreme hypotension 60/40mmHg, tachycardic with heart rate around 160 beats per minute, tachypneic with breath rate of 18 per minute, pale and drenched in sweat. The abdomen was diffusely tender, guarded and distended, suggestive of an acute surgical condition. Heteroanamnestic data obtained from the ambulance physician

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Correspondence to:
Dejan STEVANOVIĆ
Department of General Surgery
Zemun University Clinical Hospital Center
9 Vukova St.
Belgrade 11080, Serbia
drdejanstevanovic@gmail.com

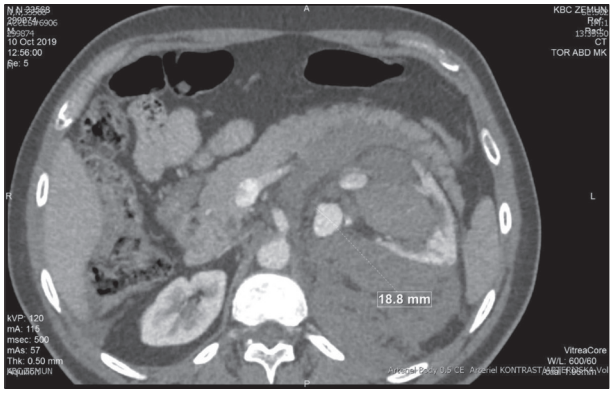

Figure 1. Large retroperitoneal hematoma on the left (axial computed tomography section) involving both the perirenal and pararenal space; aneurysmal dilatation of the left renal artery up to 18.8 mm in diameter

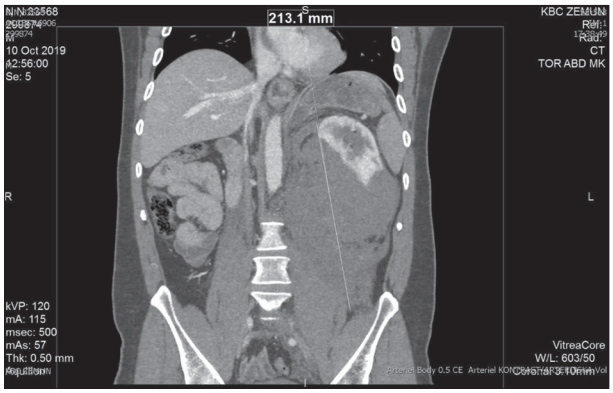

Figure 2. Large hematoma of the retroperitoneum on the left (coronal computed tomography section), with the largest intercommissural diameter up to 213 mm

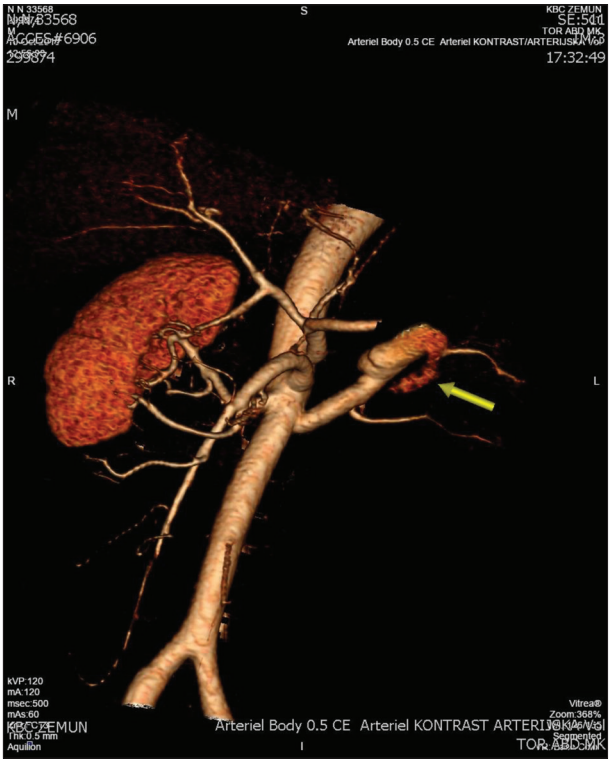

Figure 3. Virtual reality 3D imaging angiographic view of the aorta; there is a large fusiform aneurysmal dilatation of the terminal part of the left renal artery (after separation of a separate branch for the lower part of the kidney) with rupture of the lower branch of one of the middle interlobar arteries, with arrow marking the site of contrast extravasation into the hematoma around the left kidney

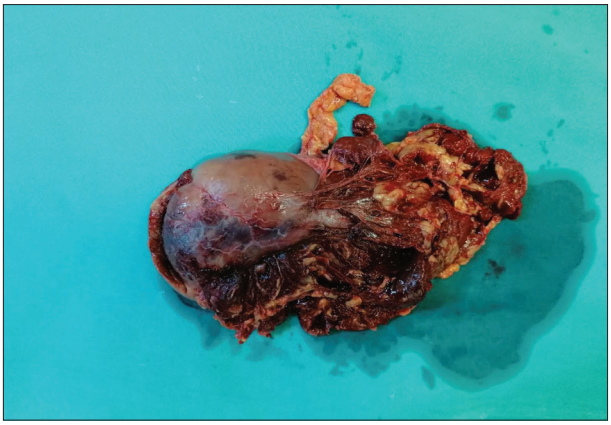

Figure 4. The destruction of the lower pole of the left kidney, as a source of massive bleeding

suggested that the patient had gross hematuria immediately after a sudden onset of severe left flank pain during an intense physical activity. Further data were not available. A Foley catheter was inserted and around 500 ml of bloody urine was obtained, along with small blood cloths. Due to the high suspicion of internal bleeding, the patient was sent for an emergency computed tomography (CT) scan, which was performed without and after intravenous injection of a contrast medium. Meantime, blood analysis results revealed hemoglobin at 7.2 g/dl (14–17.5), creatinine at 1.5 mg/dl (0.7–1.2), and urea at 49.8 mg/dl (12.8–42.8). CT finding in the arterial phase indicated tortuous and up to 18.8mm dilated left renal artery with active contrast extravasation into the left retroperitoneal space from its inferior segmental branch and the intraperitoneally large amount of free fluid of blood consistency (Figure 1).

The CT scan also demonstrated a rupture of a large retroperitoneal hematoma with massive intraperitoneal hemorrhage. The left kidney was pushed cranially towards the spleen by a massive hematoma that occupied the entire left retroperitoneal space, measuring almost 220 mm in length, and propagated perirenally, pararenally, and partially to the contralateral side (Figure 2).

A giant cyst of the lower kidney pole with diameter up to 80 mm was also reported. The pyelon, left ureter, and urine bladder were completely filled with blood. Active bleeding was detected at the time of the angiogram (Figure 3).

The patient was rushed to the operating room, where a life-saving nephrectomy was performed, while intraperitoneal hemorrhage and retroperitoneal hematoma was evacuated. The estimated blood loss was around 2500 ml. Nine units of blood and 10 units of blood plasma, cryoprecipitate, and platelets were administered intraoperatively, each. Later, examination of the removed kidney verified the destruction of its lower pole, while the rest was not pathologically altered (Figure 4).

The postoperative course was uneventful and the patient was discharged fully recovered after 14 days, with normal diuresis and serum levels of creatinine and urea

within referential values. During the period of hospitalization, he was diagnosed with hypertension.

Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Renal artery aneurysms including pseudoaneurysms represent localized anomalous dilations of the renal artery or its branches. Once thought rare, today they are discovered with increasing frequency due to unrelated abdominal imaging or on screening work-ups for hypertension, as well as widespread use of angiography. Overall incidence ranges 0.01–1%, and increases up to 2.5% in hypertensive patients, and can be as high as 39% in patients with hypertension unresponsive to therapy. The average age at diagnosis is 40–60 years. They occur more frequently in men, and are primarily located on the right side. They can be congenital or acquired. Congenital aneurysms are associated with autosomal dominant disorders, such as polycystic disease. Acquired etiologies include long-standing and untreated hypertension, atherosclerosis, trauma, inflammation, renal surgical manipulation (open, laparoscopic, or endovascular), malignancy, irradiation, coagulopathy, etc. [10–14]. Clear pathophysiology is yet uncertain, but their development is reported to be related to atherosclerosis and fibromuscular dysplasia in 60% of the cases, and to renal arterial hypertension in 25% of the cases [15, 16].

RAP arises from the disruption of renal artery wall continuity. At first, a combination of hypotension, coagulation, and sufficient compressive force exerted by the surrounding tissue, such as adventitia, renal parenchyma, and Gerota's fascia, results in decrease and cessation of the bleeding. Later, dissolution of the blood clot results in restoration of the normal blood flow and communication between the intravascular and extravascular space, leading to the formation of a pseudoaneurysm. In time, pseudoaneurysm can grow in size and eventually become unstable, susceptible to rupture [17].

Signs and symptoms may include hematuria, anemia, flank pain or abdominal tenderness, pulsatile abdominal mass and shock. They may develop immediately after the lesion occurred or may be delayed, as reported by several studies [17, 18]. Hematuria is the most common symptom which results from the erosion into the adjacent renal collecting system [18]. However, patients with RAP may present with nonspecific symptoms, may be completely asymptomatic, or may not have any medical history related to RAP, thus making diagnosis challenging due to potential lack of suspicion from physicians.

Bearing in mind all of the above, and in the case when patient presents with one or several complications, physicians need to be aware of them and to act quickly, given a high mortality rate in case of rupture, which is up to 80% [17, 18, 19].

Diagnosis of RAP is primary radiologic, either if discovered incidentally or due to suspicion in the presence of a complication. Doppler ultrasound may indicate the existence of aneurysm or pseudoaneurysm, as well as the active hemorrhage and existing hematoma. Contrast CT scan can confirm the aneurysmal dilatation and define its anatomic details, and can also demonstrate active extravasations of contrast in case of bleeding and quantify the retroperitoneal hematoma. Angiography is the imaging modality of choice [20].

In our case, a male patient with no prior history of surgery, significant abdominal trauma and systemic disease, presented with left flank pain and signs of hypovolemic shock that manifested before the admission in the surgical emergency room. The CT scan promptly demonstrated a rupture of a large retroperitoneal hematoma with massive intraperitoneal hemorrhage. Angiography confirmed the rupture of the RAP.

Methods of managing RAP are also a challenging issue. A few modalities have been exploited so far. Depending on the patient's clinical condition, RAP can be treated by nephrectomy, open vascular surgery, endovascular treatment, or angiographic embolization [21, 22, 23]. The urgent surgical indications include overt ruptures, existing renal damage, expansion of the aneurysm, and renovascular hypertension. It is suggested that angiographic embolization is the procedure of choice for RAP management due to its minimally invasive and selective nature along with maximal preservation of the renal parenchyma; surgery remains a very important treatment in case of a RAP, particularly in the presence of hypovolemic shock [24, 25]. In our case, a left nephrectomy was performed due to the urgency of the entire procedure, large blood loss, and a large destroyed area of the renal parenchyma. Prior to performing the nephrectomy, we had to evacuate large retroperitoneal and intraperitoneal hematomas with vascular control of the abdominal aorta. In this situation, minor invasive procedures were unacceptable, so left nephrectomy was the surgery of choice in our case.

Even though RAP is a rare entity, physicians may come across it during their work. Rupture of pseudoaneurysms with subsequent hemorrhage into the intraperitoneal cavity and retroperitoneum is a life-threatening condition, as proven in the presented case, in which hypovolemic shock manifested itself before the admission. Therefore, we would like to highlight the importance of high blood pressure control and of regular check-ups.

Conflict of interest: None declared.

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Редак случај спонтане руптуре псеудоанеуризме бубрежне артерије код претходно хипертензивног болесника

Дејан Стевановић[1,2], Небојша Митровић[1,2], Дамир Јашаровић[1,2], Александар Лазић[2], Бранко Лукић[2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клиничко-болнички центар „Земун", Клиника за хирургију, Служба опште хирургије, Београд, Србија

САЖЕТАК

Увод Псеудоанеуризма бубрежне артерије или њених сегментних грана је ретка и обично асимптоматска васкуларна лезија, која у већини случајева спонтано тромбозира. Истовремено, она може руптурирати и довести до животно угрожавајућег крварења и стања хиповолемичног шока. Данас се ове псеудоанеуризме откривају задесно у склопу широко распрострањене КТ ангиографске дијагностике неког другог абдоминалног патолошког стања или током скрининга на хипертензију. Типично се примећују код болесника након трауме, упалних процеса, бубрежне операције или биопсије. **Приказ болесника** Педесетдвогодишњи болесник мушког пола без претходне историје хирургије, значајне трауме стомака и системске болести, примљен је као хитан случај са јаким боловима у левој половини трбуха и знаковима хиповолемичног шока. Хитна комјутеризована томографија је показала руптуру великог ретроперитонеалног хематома са масивним интраперитонеалним крварењем. КТ ангиографија је потврдила рутпуру псеудоанеуризме бубрежне артерије која је дисецирала према доњем полу левог бубрега. Болесник је хитно оперисан, када је урађена лева нефректомија уз евакуацију велике количине слободне свеже крви и коагулума интраперитонеално, као и ретроперитонеалног хематома. Четрнаест дана након операције болесник је отпуштен потпуно опорављен, са нормалном диурезом и нивоом креатинина и урее у серуму унутар референтних вредности. Током периода хоспитализације дијагностикована му је хипертензија, која је медикаментозно искоригована. **Закључак** Руптура реналне псеудоанеуризме са крварењем у интраперитонеалну дупљу и ретроперитонеум је животно угрожавајуће стање, што је показано у нашем случају, у којем се хиповолемијски шок манифестовао приликом пријема. Посебно истичемо важност контроле високог крвног притиска и медикаметозног третмана оваквих болесника.

Кључне речи: псеудоанеуризма бубрежне артерије; руптура; крварење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Solitary cecal ulcer – case report and treatment options according to literature review

Vanja Kunkin, Aleksandar Ognjenović

Đorđe Joanović General Hospital, Department of General Surgery, Zrenjanin, Serbia

SUMMARY

Introduction Solitary cecal ulcer is a benign and extremely rare disease, as less than 300 cases have been reported so far. The etiology is unknown, and it can be diagnosed by a pathohistological examination. Often presented as an acute abdomen and rectal bleeding, it can mock various important and urgent conditions. Treatment protocol is not defined. Extensive and radical surgeries are often performed due to this benign disease mimic. Our aim was to indicate this disease, present the treatment, and to facilitate the treatment plan for the disease.

Case outline A 67-year-old female patient was admitted to the Emergency Department with a clinical manifestation of acute appendicitis. Emergency surgery was indicated by the diagnostic tests. The intraoperative finding revealed an ulcer on the cecum, which was sutured. The patient fully recovered, and subsequent colonoscopy and pathohistological findings indicated a solitary ulcer.

Conclusion It is possible to treat this condition by retaining the organ and avoiding major surgery. Therefore, it is our opinion that it might provide significant assistance to clinicians in a similar situation. Hence, it is undoubtedly an interesting case for archiving, especially since such a case had not been recorded in our country previously.

Keywords: ulcer; rare disease; cecum; colonic disease

INTRODUCTION

Solitary cecal ulcer (SCU) is a rare, benign, and specific entity. It is described only as a case report or, in some rare cases as case series. SCU is the ulcer of the cecum without common etiology following pathohistological examination. Between 250 and 350 cases of solitary colonic ulcers have been reported in the world thus far, whereas just over 258 cases have been detected in the cecum. It was noted in subject-specific medical publications that about 67% of this disease affects the cecum, 18% transverse colon, hepatic, and splenic flexure, and 15% descending and sigmoid colon [1].

Cruveilhier described SCU for the first time in 1832 [2, 3]. It is a rare disease and it can easily be superseded by acute appendicitis or colonic neoplasm. In most cases, it can involve conservative treatment rather than surgical, except in cases of perforation, obstruction, and uncontrolled bleeding. The dominant symptom is a pain in the lower right quadrant of the abdomen. It is diagnosed as an acute appendicitis in 50% of cases. It can be identified as lower gastrointestinal hemorrhage (33%), visceral perforation (19%), or palpable abdominal mass (16%) [1, 3].

Physical examination in most cases reveals tenderness in the lower right quadrant of the abdomen, and in some cases it might be reflected as an acute abdomen or rectal bleeding. Laboratory tests are nonspecific; inflammation markers can be elevated, blood count may be lowered, tumor markers are not elevated. Radiographic imaging is usually nonspecific or it can show bowel obstruction or pneumoperitoneum due to perforation. Ultrasound of the abdomen is also nonspecific or it can show a mass in the cecal region. Computed tomography usually shows wall thickening of the cecum. The best way to diagnose SCU is by conducting colonoscopy screening, followed by a pathohistological examination of a biopted or resected sample. Findings are usually nonspecific chronic inflammation, and rarely an acute inflammation. There is no substantial reasoning about etiology in these samples. It is speculated that long-term use of non-steroidal anti-inflammatory drugs (NSAID) is the main causative agent of SCU.

The typical position of the ulcer is lateral, anti-mesenteric, on the cecum wall, 2 cm cranial from the ileocecal valve [4, 5, 6].

For this study, it was of interest to point out this disease, to present how we have managed this rare condition, and to contribute to defining a treatment protocol for this disease.

CASE REPORT

A 67-year-old female patient was admitted to the Emergency Department with the main complaint of severe pain in the right lower quadrant of the abdomen. The pain started two weeks before the admission, when the pain became unbearable. She experienced nausea

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Correspondence to:
Vanja KUNKIN
Cara Lazara 25
Zrenjanin
Serbia
kunkinbre@gmail.com

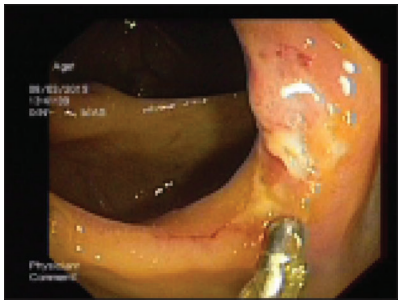

Figure 1. Colonoscopy finding before biopsy

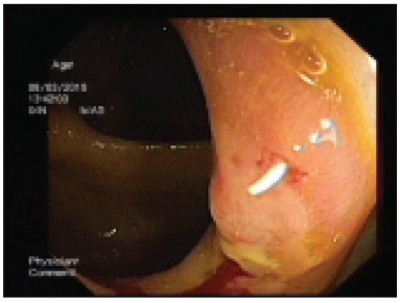

Figure 2. Colonoscopy finding after biopsy

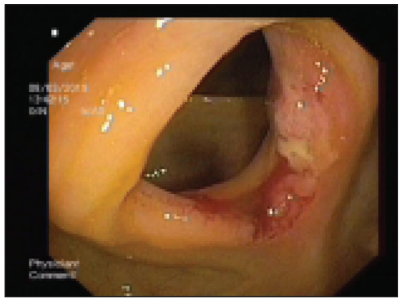

Figure 3. Colonoscopy finding after biopsy

and vomiting. Rectal bleeding, weight loss, and other complaints were not detected. The patient reported several comorbidities – hypertension, ischemic cardiomyopathy, diabetes mellitus, and previous myocardial infarction. The patient regularly used the following medicines: isosorbide mononitrate, trimetazidine, a combination of clopidogrel and acetylsalicylic acid, the combination of ramipril and felodipine, bisoprolol, atorvastatin, metformin, and gliclazide. She neither smoked for the last eight years nor used alcohol.

The patient's health status, on admission, was good – she was normotensive, afebrile, with normal heart rate and blood oxygen saturation. During palpation, we discovered tenderness in the lower right quadrant of the abdomen and rebound pain, with peritoneal irritation and without abdominal rigidity. There were no other signs of the aforementioned condition, and the rest of the clinical findings were satisfactory. Laboratory tests showed an elevated number of white blood cells, 19.3×10^9/L with predomination of granulocytes 85% or 16.6×10^9/L, elevated glycemia 9.32 mmol/L, and C-reactive protein 106 mg/L; on the other hand, hemoglobin and hematocrit were lowered: 114 g/L and 34.4%, respectively. There were no pathological changes in the urine. Ultrasonography of the abdomen and urinary system showed cholecystolithiasis (without inflammation), meteorism, dilatation of the right pyelocalyx (grade I), without other pathological changes; however, the appendix could not be displayed. Abdominal radiography showed meteorism with hydroaeric level in the right iliac fossa. The emergency surgery was indicated due to suspected acute appendicitis with the risk of perforation.

Intraoperatively, a small amount of turbid whitish fluid was found, however, the swab test was sterile. There was an ischemic field on the lateral cecal wall, with an approximate diameter of 35 mm. Those areas were thin, dark, and deserosed with signs of local peritonitis and reactive appendicitis. We stitched that field in two layers with polydioxanone 3.0 suture in a continued and interrupted manner. Following appendectomy, flushing and drainage were applied. During the postoperative period, the patient was hemodynamically stable, afebrile, in good overall condition with satisfactory local findings. Laboratory tests showed a decline in inflammatory markers. The patient was discharged from the hospital after seven days, receiving a recommendation for further therapy and a colonoscopy screening in two months. The overall condition of the patient was satisfying during subsequent check-ups. Three weeks after the surgery, the results of pathohistological analysis of the appendix showed fibrous obliteration of the appendix lumen. Three months after surgery, the pathohistological analysis of findings of suspected biopted change observed during the colonoscopy showed a separation of the wide and shallow lesion on the fold in front of the valve, resembling an ulcer covered with fibrin; the rest of the colon and rectum were free of pathological changes (Figures 1, 2, and 3).

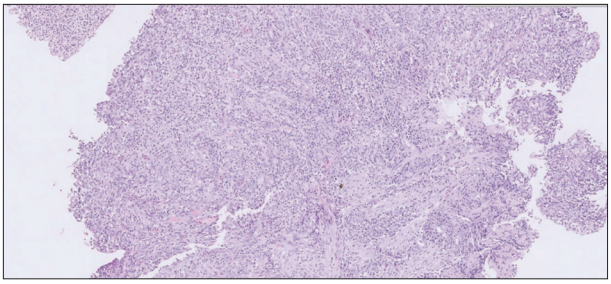

Figure 4. The bottom of the ulcer (H&E, × 10)

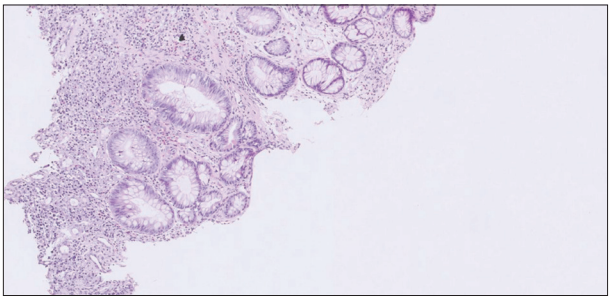

Figure 5. Colonic mucosa with dystrophic crypts and laminae propriae fibrosis in the lower part of the image (H&E, × 10)

The pathohistological finding of Prof. Slavica Ušaj, M.D. (pathologist, subspecialist cytologist) was as follows: the samples consist of fragments of necrotic detritus and fragments of colonic mucosa with ulceration of the entire thickness of the mucosa; the bottom of the ulcer makes nonspecific granulation tissue imbued with a mixed inflammatory infiltrate; in the surrounding mucosa, crypts are distorted and lined with regenerative epithelium, elongated and pseudo-stratified nuclei; one focus loses maturation to the surface and the same type of change is found in a small portion of the superficial epithelium. Therefore, she concluded that it was a solitary cecal ulcer with the focus of low-grade dysplasia (Figures 4 and 5).

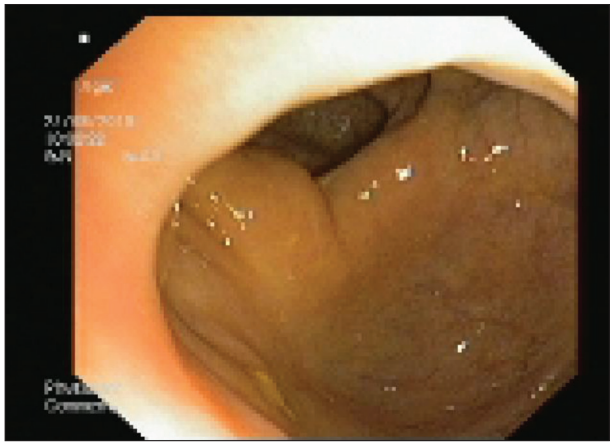

Figure 6. Control colonoscopy finding

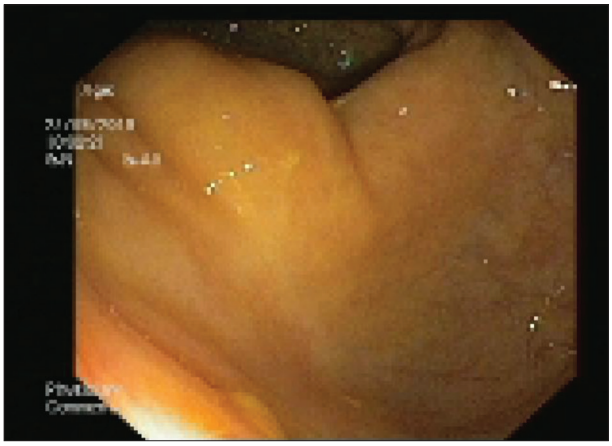

Figure 7. Control colonoscopy finding

Six months after the surgery, the patient did not experience any pain. She went for a control colonoscopy screening nine months after the surgery. The findings showed complete healing of the ulcer, the mucosa had normal appearance; laboratory findings were within the reference ranges, except for the blood count, which was slightly lower than the lower limit of the reference values (Figures 6 and 7).

For the publication of this case, we received written consent of the patient and the Hospital Ethics Committee No 01-797/9.

DISCUSSION

Referencing the available literature, we discovered a total of 258 reported cases of solitary cecal ulcer. We searched through PubMed database (148 cases reported in case reports and case series), Google Scholar database (110 cases reported in case reports and case series), Cochrane database (there were no systematic reviews and meta-analyses about solitary cecal ulcer), and Scopus database (no reports). We were looking for cases of a cecal ulcer and a solitary cecal (coecal) ulcer (ulcus) in these databases and in the references of the publications that we found. We excluded transplanted patients due to an altered immune system, in which the cause of the ulcer is usually cytomegalovirus (CMV) [5]. Transplanted and dialysis patients have a high mortality rate (50%) if surgery is required [7].

Our patient was a 67-year-old female; analysis of other studies and their findings indicate that the sex ratio is usually 50:50 [8, 9]. The median age that we found in the case series and reports is 57 years, which is similar to the results of some studies that represented age predilection of 40–60 years [1] or age median of 61 years [8].

The clinical appearance and laboratory findings of our patient suggested that she suffered from acute appendicitis. Emergency surgery was indicated. Colonoscopy or resection of the specimen is necessary for pathohistological confirmation, which is the only method to confirm this entity. In our case, it was not indicated because of the clinical picture of the acute abdomen and the risk of potential complications it brings along, as well as because of the complexity of delivery in unprepared patients. In any other case – rectal bleeding, suspected tumor, pain of unclear etiology – colonoscopy is crucial [3].

We opted for laparotomy instead of laparoscopy due to suspected perforation and purulent peritonitis. We were surprised by the findings since the change on the cecum wall was not clear to us, and our first thought was ischemia due to micro-embolization or the action of some aggressive agent. The limitation of change was clear and proper. There was no perforation.

According to some authors, a possible etiology of SCU is limited ischemia, caused by vasculitis and/or microembolization of the terminal branches of the colon nutritional arteries [9, 10]. The most frequently mentioned cause of SCU are NSAID drugs [11], but we found only a few cases of SCU in patients on NSAID therapy. For other patients, it is either unknown whether they used NSAID or not. Our patient also did not use NSAIDs, but she used acetylsalicylic acid for several years.

We decided to preserve the colon and provide the lesion with seromuscular sutures in two layers. The integrity of the wall, the vital edges of the ulcer, and the absence of a palpable tumor were reasons to think that suturing the ulcer and preserving the colon was a good solution, and perhaps the best one. The appendectomy was executed due to inflammatory altered walls. It was most likely a consequence of regional inflammation. Two authors performed similar surgery in cases of SCU with the clinical findings of appendicitis or perforation [12, 13]. In the earlier period, surgical treatment of this entity was insisted on [14], while in recent times, conservative treatment has been favored, except in cases of perforation, uncontrolled bleeding, or acute abdomen [4, 15]. The range of applied operations is wide. The most common is right hemicolectomy, open or laparoscopic, about 41% of all operations duo to SCU according to the available literature [16]. Other operations – segmental resection and stoma, ileocecectomy and anastomosis, cecostomy due to perforation, laparoscopic or open sleeve cecectomy, open or laparoscopic-assisted ulcer excision, or even total colectomy – are rarely performed. Conservative therapy includes symptomatic therapy, blood replacement if necessary, and regular colonoscope monitoring, but without exactly specified intervals. Two authors

presented two successful treatments with antibiotics, ciprofloxacin, and metronidazole [4, 9].

A big problem is pathohistological confirmation, as it is the only way to confirm SCU with certainty. The acute condition represents an even larger issue. In most such cases, pathohistological confirmation is not possible. Also, there is a growing possibility that a larger and more radical operation will be performed due to benign disease. It is very difficult to prevent such an outcome. According to the experience of several authors so far, in cases of accidental discovery, pathohistological verification and conservative treatment is the best option. But the question what to do in case of an acute condition remains.

Our case confirmed that minimal surgical intervention with organ preservation is possible. The organ and its function can be preserved completely, facilitating a better quality of life for the patient. A significant benefit is that there is less chance of complications which happen after major resection procedures, such as non-healing of the anastomosis, enteral fistula, peritoneal cavity infection, wound infection, septicemia, multi-organ failure, and death. Lesser invasiveness and lower number and extent of complications decrease the treatment expenses, duration of hospitalization, increase the odds for positive treatment outcome and shorten the period of recovery, thus enabling an earlier return to regular daily activities.

Colonoscopy monitoring and pathohistological verification is mandatory after the intervention. It remains to determine time intervals. The main dilemma remains as to when malignancy is suspected in acute conditions – whether it is justified to take a clip and do an extempore biopsy, or should we adhere to oncological principles. On the one hand, it is a quite rare entity, and the possibility of malignity is very high; on the other hand, what matters most is each patient's life and its quality.

Conflict of interest: None declared.

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Солитарни улкус цекума – приказ случаја и терапијске могућности према прегледу литературе

Вања Кункин, Александар Огњеновић

Општа болница „Ђорђе Јовановић", Одељење опште хирургије, Зрењанин, Србија

САЖЕТАК

Увод Солитарни улкус цекума је бенигно и екстремно ретко обољење; до сада је пријављено мање од 300 случаја. Узрочник обољења је непознат, а може бити потврђено само патохистолошким испитивањем. Често је презентовано као акутни абдомен и ректално крварење, а може имитирати и разна друга битна и ургентна стања. Не постоје протоколи лечења за ово обољење, а често се изводе велике и радикалне операције због њега.

Наш циљ је да представимо како смо решили један такав случај.

Приказ болесника Жена старости 67 година примљена је у Ургентни центар са сликом акутног апендицитиса. Након урађене дијагностике индикована је хитна операција. Интраоперативни налаз је указивао на улкус цекума, који смо прешили, чиме смо сачували орган. Болесница се у потпуности опоравила, а каснији колоноскопски и патохистолошки налаз је показао да је у питању солитарни улкус цекума.

Закључак Могуће је сачувати орган и избећи већу операцију код постојања овог обољења. Мишљења смо да би овај случај могао помоћи клиничарима који се нађу у сличној ситуацији. Свакако, случај је занимљив за архивирање, поготово што у нашој земљи још није забележен овакав случај.

Кључне речи: улкус; ретко обољење; цекум; обољење колона

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Case report of a patient with toxic epidermal necrolysis with complications and review of literature

Dragana Petrović-Popović[1], Mirjana Petrović-Elbaz[2]

[1]University Clinical Center of Serbia, Clinic for Burns, Plastic and Reconstructive Surgery, Belgrade, Serbia; [2]James J. Peters Department of Veterans Affairs Medical Center, New York, NY, United States of America

SUMMARY

Introduction Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a rare exfoliative disorder with a high mortality rate. This entity was first described by Lyell in 1956, who termed the condition 'toxic epidermal necrolysis,' pointing out that drug sensitization was generally considered to be the mechanism leading to this syndrome. The drugs most frequently involved are nonsteroidal anti-inflammatory drugs (NSAID), chemotherapeutic agents, antibiotics, and anticonvulsants, although viral, bacterial, and fungal infections, as well as immunization, have been described.

Case outline We present a 72-year-old man with the following history. Five days before he was admitted, the patient had high fiver and sore throat. He was treated with antibiotics and NSAID because he had bronchopneumonia, after which he developed itchy skin rash all over his body, followed by the sensation of slight sore throat, with conjunctival hyperemia and hard breathing and high fiver, due to which he was hospitalized in the local hospital. After worsening of the symptoms, followed by urticaria-like plaques and bullae with progress all over the body, the patient was moved to our institution and placed in the Intensive Care Unit, under suspicion of TEN. The aim of the paper presented here is to give a thorough summary of our literature review searching for the best therapy modalities for our patient with TEN.

Conclusion Our standpoint is that TEN patients with multiorgan system lesions, with 80% of the total body surface area affected, and with SCORTEN scale score of 4 can be successfully treated if diagnosed early.

Keywords: toxic epidermal necrolysis; drug induced TEN; intensive care unit

INTRODUCTION

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is rare exfoliative, life-threatening disorder, drug-induced, mucocutaneous disease, with high mortality rate. This entity was first described by Lyell [1] in 1956, who termed the condition 'toxic epidermal necrolysis,' pointing out that drug sensitization was generally considered to be the mechanism leading to this syndrome. Stevens–Johnson syndrome (SJS) was first described in 1922 by Stevens and Johnson [2] in a report of two young boys, as an acute mucocutaneous syndrome with eruptive fever, stomatitis, and ophthalmia. The drugs most frequently involved are nonsteroidal anti-inflammatory drugs (NSAID), chemotherapeutic agents, antibiotics, and anticonvulsants, although viral (herpes simplex virus), bacterial (*Mycoplasma pneumoniae*), and fungal infections, as well as immunization, have also been listed. Well known drugs that can induce TEN or SJS are the following: allopurinol, trimethoprim-sulfamethoxazole, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital, and NSAIDs. Recent studies suggest that several drugs, such as carbamazepine and allopurinol, are reported to have a strong relationship with a specific human leukocyte antigen type. This relationship differs between different ethnicities [3, 4]. TEN and SJS are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment [3].

The incidence of TEN is very low (1–2 cases per one million people), but reported mortality rates vary 20–60%. Although a study in the USA indicated that the incidence rate is 1.58–2.26 cases per one million people, the overall incidence of SJS/TEN remains unclear [4, 5]. Some studies of HIV-positive patients show a much higher incidence rate than in other populations. Disease severity and prognosis can be further delineated utilizing the SCORTEN criteria [6, 7].

The pathogenesis of TEN is still not fully clear. The widespread epidermal death is thought to be a consequence of keratinocyte apoptosis. The majority of studies focus on the role of T cells. Recent studies indicate that TEN may be an MHC-class-I-restricted specific drug sensitivity resulting in clonal expansion of CD8+ cytotoxic lymphocytes with a potential for cytolysis. Dysregulation of the tumor necrosis factor (TNFα) system is also likely to be involved in TEN pathogenesis. Functional studies showed that FAs-L was typically active on keratinocytes in TEN. The expression of Fas-L on human keratinocytes is upregulated

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Correspondence to:
Dragana PETROVIĆ-POPOVIĆ
University Clinical Center of Serbia
Clinic for Burns, Plastic and Reconstructive Surgery
Stanoja Glavaša1a/8
11000 Belgrade, Serbia
draganapetrovicpopovic@gmail.com

by cytokines including IL-1β, Il-15, IFN-Y, and TNF-α realized by keratinocytes themselves and also by skin-infiltrating immunocompetent cells [8–11].

The clinical course of TEN is characterized by a prodromal phase with influenza-like symptoms, followed by intense erythema, urticarial plaques, and bullae with progress over a day or two to a more generalized epidermal slough, with involvement of the mucosal surfaces. Progressive neutropenia and thrombocytopenia may develop within a few days and, together with septic complications, may lead to multiorgan failure and death. The severity-of-illness score for TEN (SCORTEN) is a measure of severity of illness for toxic epidermal necrolysis. The score is determined by the number of present risk factors. The higher the score is, the greater the mortality rate for the patient. The presence or absence of seven risk factors is used to determine the SCORTEN: (1) age > 40 years, (2) malignancy, (3) total body surface area affected > 10%, (4) heart rate > 120 beats per minute, (5) blood urea nitrogen > 28 mg per dl; (6) serum glucose > 250 mg per dl; (7) serum bicarbonate < 20 mEq per l. The absence of a risk factor is scored as zero; the presence of a risk factor is scored as one. SCORTEN ranges 0–7 [3].

The aim of the paper presented is to give a thorough summary of our literature review searching for the best therapy modalities for our patient with TEN.

Figure 1. Patient photograph on admission

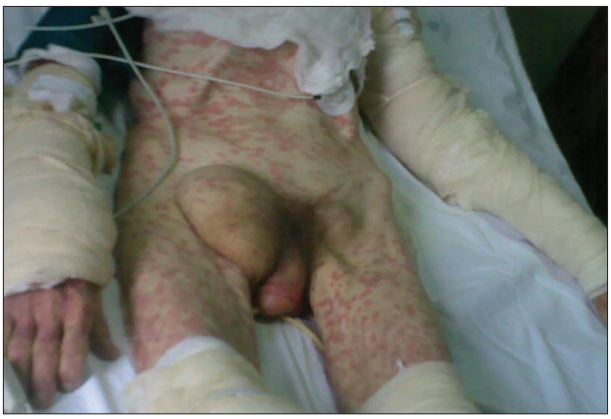

Figure 2. Patient photograph – closer view on the patient's rash on admission

CASE REPORT

We present a 72-year-old man from small town who presented with five days of high fever and sore throat and was diagnosed with bronchopneumonia. The patient was treated with antibiotics (amoxicillin and gentamicin) and NSAID. After five days, the patient developed itchy skin and rash all over his body, followed by sore throat, conjunctival hyperemia, and difficulty in breathing. He was initially hospitalized in the local hospital. After worsening of symptoms followed by urticaria and bullae with progression all over his body, the patient was hospitalized at our institution, in the Intensive Care Unit, under suspicion of TEN.

In the Intensive Care Unit, physical examination revealed 80% of the total body surface area (TBSA) was affected with severe bullous skin changes, followed by conjunctival hyperemia, eyelid edema, oral mucosae erosions, edema of the tongue, auricula of the ear and the external ear canal, with de-epithelization of the skin. Severe balanitis was observed as well. The patient had difficulty speaking due to the oral mucosa lesion, and with 80% of the TBSA affected with severe bullae, which gave us a picture of a superficial major scald burn that affected 80% of the TBSA. The examination of the eyes by an ophthalmologist found de-epithelization of the borders of the eyelids with corneal epithelium lesion. The patient was examined by an otorhinolaryngologist and was found to have ulcerations and erosions in the vestibule of the nares, the oral cavity, and the tongue, hyperemia of the epiglottis and the hypopharynx. Additional laboratory analyses, such as *Treponema pallidum*, *M. Pneumoniae*, HIV, HBSAg, anti HCV, were all negative. Chest X-ray revealed diffuse opacity, more intensive at the basis of the lungs, which correlated with bronchopneumonia. Laboratory findings were as follows: white blood cell count 10.5; red blood cell count 4.26; hemoglobin 124; hematocrit 0.37; platelet count 340; C-reactive protein 130.1; coagulation panel was normal.

The patient had a history of seizures, chronic obstructive pulmonary disease, gastroesophageal reflux disease. His home medications were phenobarbital, aminophylline, and ranitidine.

We started major second-degree burn injury treatment, with fluid resuscitation according to the modified Burk formula. The patient was positive for Nikolsky's sign between affected skin lesions. Local treatment included wound debridement and application of petroleum jelly gauze and boric acid solution, every-day wound debridement and bandage, antibiotic therapy with vancomycin and cefepime according to sensitivity. Corticosteroids were excluded due to wound healing. We stopped phenobarbital and NSAID as they could possibly exacerbate TEN.

Our patient did not require mechanical ventilation. SCORTEN scale score on day one was 4, which remained the same on day three – SCORTEN scale score represented high mortality rate risk. A skin biopsy confirmed the diagnosis of TEN. After intensive treatment we noticed a decrease of rash and partial epithelization with skin pilling in the areas which were not involved.

We obtained verbal and signed consent of the patient to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki.

DISCUSSION

TEN is an acute, life-threatening, exfoliative disorder with high mortality rate. High clinical suspicion, prompt recognition, and initiation of supportive care are mandatory. Once diagnosed, the management of SJS/TEN focuses primarily on supportive care and wound management with the addition of adjunctive medications. Thorough investigation of the pathogenic mechanisms is fundamental. The definitive management of SJS/TEN remains to be established. Supportive care is the most universally accepted intervention for SJS/TEN.

Granulysin and CCL-27 serum markers are elevated in patients with SJS/TEN and can be helpful markers to monitor disease severity, as reported in some recent studies [12, 13, 14]. Further research is required before these markers can be reliably used for diagnosis [15, 16].

A recently published study shows a possible connection between TEN and a positive diagnosis of COVID-19 [17].

Furthermore, even after recovery, sequelae such as blindness remain in some cases [4, 12]. Approximately 50% of SJS/TEN patients diagnosed by dermatologists and/or in burn units suffer from severe ocular complications such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects in the acute stage. In the chronic stage, this results in sequelae such as severe dry eye and visual disturbance [13].

Specific guidelines differ from the care required for patients with thermal burns. The effective use of intravenous immunoglobulin (IVIg) therapy for a part of the disease spectrum is not well documented. A consensus regarding combined corticosteroids and IVIg has not been reached. However, optimal therapeutic options such as systemic corticosteroids, IVIg, cyclosporine, and TNF-α antagonist are still controversial. Recently, the beneficial effects of cyclosporine and TNF-α antagonists have been explored [8, 12].

Further studies to elucidate the pathogenesis of SJS/TEN are needed.

We decided to present this case because our patient had been affected with lesions in multiorgan systems with superficial major scald burns affecting 80% of the TBSA, with successful outcome. While supportive care measures may seem an obvious aspect of SJS/TEN patient care, providers should understand that these interventions are imperative and that they differ from the care recommended for other critically ill or burn patients.

Conflict of interest: None declared.

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Приказ болесника са токсичном епидермалном некролизом са компликацијама и преглед литературе

Драгана Петровић-Поповић[1], Мирјана Петровић-Елбаз[2]

[1]Универзитетски клинички центар Србије, Клиника за опекотине, пластичну и реконструктивну хирургију, Београд, Србија;
[2]Медицински центар Одељења за бригу о ветеранима „Џејмс Џ. Питерс", Њујорк, Сједињене Америчке Државе

САЖЕТАК

Увод Токсична епидермална некролиза (ТЕН), позната и као Лајлов синдром, ретко је ексфолијативно обољење са веома високом стопом смртности. Овај ентитет је први описао Лајл 1956. године, и овај термин описује стање „токсичне епидермалне некролизе", апострофирајући на медикаметозно узроковану сензитивност као водећи механизам овог синдрома. Медикаменти који су најчешћи узрок овог синдрома су нестероидни антиинфламаторни лекови, хемотерапеутици, антибиотици, антиконвулзиви, али и вируси, бактерије и гљивице, као и имунизација.

Наш циљ је био да прегледом најновије литературе пронађемо оптималне терапијске модалитете за нашег болесника са ТЕН.

Приказ болесника Болесник, мушкарац старости 72 године, имао је бронхопнеумонију и повишену температуру пет дана, праћену болом у грлу. Лечен је антибиотицима и нестероидним антиинфламаторним лековима, након чега долази до развоја оспе и свраба по целом телу, као и развоја булозних промена на кожи, промена на мукози, конјунктивалне хиперемије, отежаног дисања и високе температуре, због чега је најпре био хоспитализован у локалној болници. Због прогресије булозних промена и погоршања општег стања болесник је пребачен у терцијалну здравствену установу и лечен у јединици интензивне неге под сумњом на ТЕН.

Закључак Сматрамо да болесници са ТЕН која захвата више од 80% површине тела, *SCORTEN* скором 4 и другим органским системима уз правовремено постављену сумњу на ТЕН могу бити успешно излечени.

Кључне речи: токсична епидермална некролиза; лековима индукована ТЕН; Одељење интензивне неге

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pediatric acute disseminated encephalomyelitis associated with myelin oligodendrocyte glycoprotein antibodies

Tatjana Redžek-Mudrinić[1,2], Ivana Kavečan[1,2], Katarina Koprivšek[1,2], Goran Rakić[1,2], Jasmina Pajić[2]
[1]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[2]Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia

SUMMARY
Introduction Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are immune-mediated inflammatory conditions of the central nervous system (CNS) with a wide clinical phenotypic variability. In order to further understand the possible phenotype of MOGAD here we report a pediatric case of acute disseminated encephalomyelitis (ADEM) associated with MOG antibodies.
Case outline A previously healthy four-month-old infant presented due to a 1-day history of fever up to 39°C and vomiting. On admission, she was encephalopathic. Repetitive and frequent stereotyped dystonic movements were observed. Cerebrospinal fluid (CSF) examination showed pleocytosis (lymphocytes were predominant) and proteinorachy. CSF culture and virology results were negative. Serum MOG antibodies were positive. A prolonged electroencephalography showed continuous high-amplitude slow rhythmic activity with captured stereotyped movement. Epileptic discharges were not seen. Although magnetic resonance imaging showed signs of acute demyelinating encephalomyelitis, our patient did not have seizures, despite neuroimaging findings of cortical lesions. Acute treatment with the corticosteroids led to excellent response with full recovery.
Conclusion This case emphasizes the inclusion of the MOG antibodies testing in the initial work-up in children presenting with acute encephalopathy associated with demyelinating or encephalitic abnormalities on brain and/or spinal magnetic resonance imaging even when the clinical phenotype is unusual. The prompt diagnosis of MOGAD is relevant for accurate disease monitoring and treatment strategies.
Keywords: MOG-antibody; ADEM; child; movement disorder

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) are immune-mediated inflammatory conditions of the central nervous system (CNS). MOGAD result from damage to myelin oligodendrocyte glycoprotein (MOG), expressed on surfaces of oligodendrocytes and myelin sheaths in CNS [1, 2].

Autoimmunity to MOG represents a real spectrum of acquired demyelinating syndromes (ADS) with a wide clinical phenotypic variability. Typical MOGAD presentations consist of demyelinating syndromes including optic neuritis (ON) or transverse myelitis in adults and ON or acute disseminated encephalomyelitis (ADEM) in children [2, 3, 4]. Myelin oligodendrocyte glycoprotein antibodies (MOG-abs) are seen in up to fifty percent of children with ADS [5].

Brain magnetic resonance imaging (MRI) findings in pediatric ADEM with MOG-abs usually report diffuse signal changes in juxtacortical white matter, deep white matter and deep grey matter, seen on both T2 weighted and FLAIR images. More recently, the disease spectrum has been expanded due to reports of patients with MRI cortical signal changes [6].

The presence of MOG-abs is associated with a non-multiple sclerosis (non-MS) course [3]. Disease course can be either monophasic or relapsing, with subsequent relapses most commonly involving the optic nerve [7]. Because of its clinical course, it is frequently confounded with aquaporin-4 antibody (AQP4-ab) positive neuromyelitis optica spectrum disorders. Early and accurate diagnosis of these distinct conditions is very relevant as they have different therapeutic approaches and MOGAD is associated with a better outcome and a quicker response to the first line therapy [1].

In order to further understand the possible phenotype of MOGAD, here we report a case of pediatric ADEM associated with MOG-abs with a movement disorder, and without seizures, despite neuroimaging findings of cortical lesions.

CASE REPORT

A previously healthy four-month-old infant with normal antenatal profile presented a day before admission with a fever up to 39°C and vomiting, followed by acute onset of lethargy. Her consciousness rapidly deteriorated, so they came to hospital. On admission, she was drowsy with eye opening to voice and response to pain. Her vital signs were within

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Correspondence to:
Tatjana REDŽEK-MUDRINIĆ
Hajduk Veljkova 10
Novi Sad
Serbia
tatjana.redzek-mudrinic@mf.uns.ac.rs

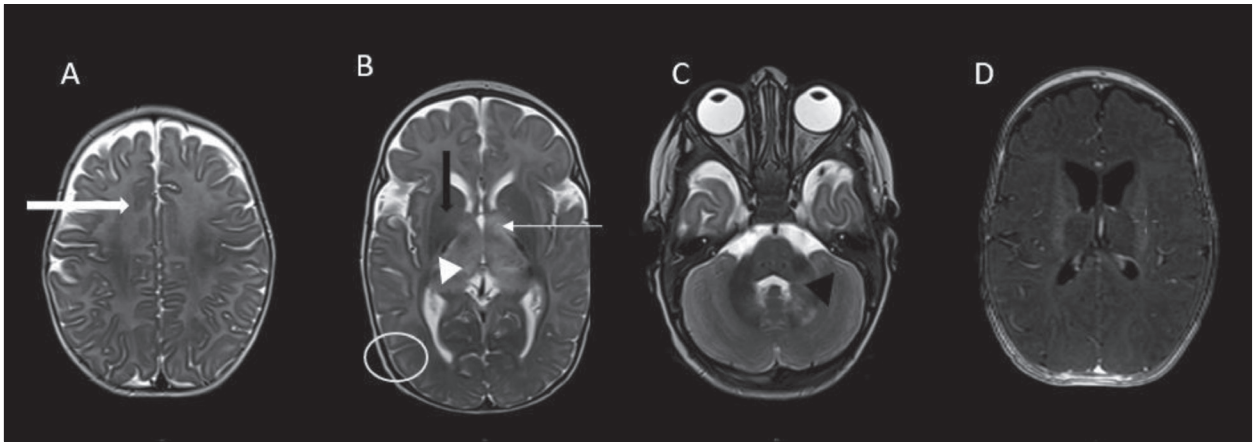

Figure 1. Brain magnetic resonance imaging demonstrating: A – cerebral oedema in supratentorial white matter (white arrow); B – segmental nonhomogeneous T2/FLAIR hyperintense lesions of thalamus (white arrowhead), right lentiform nuclei (black arrow) and posterior left internal capsule (long white arrow); the cortical disease is demonstrated in right occipital cortex (white circle); C – the lesions with similar magnetic resonance characteristics are presenting infratentorial in left middle cerebellar peduncle (black arrowhead); D – there is a mild leptomeningeal enhancement

normal range. Neurological examination revealed four-limb weakness, hyperreflexia of deep tendon reflexes and bilateral extensor plantar response. Repetitive and frequent stereotyped dystonic movements were noted, characterized by symmetrical extension of the arms and flexion of the wrists which initially responded to intravenous midazolam. Phenobarbital maintenance dose was introduced.

Routine blood and metabolic tests were within normal range. The computerized tomography scan was unremarkable. Cerebrospinal fluid (CSF) examination showed pleocytosis of 256 × 106/L (85% lymphocytes), high concentration of protein (0.67 g/L) with normal glucose, chloride and lactate levels. CSF culture, serological test for Borrelia burgdorferi and viral polymerase chain reaction test for Herpes simplex virus – 1/2 and varicella zoster virus were negative. The AQP4-abs and N-methyl-D-aspartate receptor antibodies (NMDAR-Abs) in the serum and CSF were negative. Serum MOG-abs were positive with a titer of 1:320 as well as serum and CSF oligoclonal bands, without additional bands in the CSF.

Brain MRI, on day three of admission, demonstrated cerebral oedema in the supratentorial white matter with the segmental nonhomogeneous T2/FLAIR hyperintense lesions of thalamus, and smaller lesions in the right lentiform nuclei and the posterior left internal capsule. The cortical disease was demonstrated in the right occipital cortex. The lesions with the similar MR characteristics were present infratentorial in the left middle cerebellar peduncle. There was a mild leptomeningeal enhancement. Spinal cord and optic nerve involvement were not shown (Figure 1). Three-Dimensional Time-of-Flight magnetic resonance angiography was described as normal.

A prolonged three-hour electroencephalography (EEG) showed continuous high-amplitude slow rhythmic activity 1–1.5 Hz with captured stereotyped movements. Epileptic discharges were not seen.

She was initially treated with double intravenous antimicrobials (ceftazidime and acyclovir) which were stopped after negative culture and virology results. She was given intravenous methylprednisolone (20 mg / kg / 24 h) during five days followed by oral prednisolone (2 mg/kg) weaning course over eight weeks. During glucocorticoid therapy she made a gradual clinical improvement and at two-month review she recovered almost completely, with normal mobility and no focal neurologic deficit other than using her left hand more. The control MOG-abs in serum were positive with a titer of 1:320.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines.

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the parents of the patient.

DISCUSSION

Myelin oligodendrocyte glycoprotein associated disease is a rare, antibody-mediated inflammatory demyelinating disorder of CNS with various phenotypes predominantly involving brain in the younger children. Even though the phenotype in younger children is similar to ADEM with alteration in mental status, most experts consider MOGAD as a distinct entity with different immune system pathology [8].

In our case, the poorly marginated white matter changes in an encephalopathic child made us suspect an immune-mediated encephalopathy. Although the condition resembled the diagnosis of ADEM, some of the features were not typical, in particular the cortical lesions and the movement disorder. The cortical lesions are more common in patients with encephalitis and MOG-abs presenting with increased frequency of seizures [9, 10].

The movement disorders are more frequently seen in NMDAR-abs encephalitis [11]. Brain MRI in NMDAR-abs encephalitis is usually normal. Despite basal ganglia involvement frequently described in children with MOGAD,

the movement disorder is not a cardinal feature [4, 12]. There is a case report of pediatric MOG-abs positive ADEM associated with movement disorder and seizures [13]. Our patient had a prolonged video EEG that confirmed episodes of stereotyped movements which were not epileptic. These abnormal movements stopped immediately after intravenous methylprednisolone treatment. The maintenance dose of phenobarbital was discontinued as she did not have previous seizures despite cortical lesions.

ADEM is the most frequent type of pediatric MOGAD, but there is only one study comparing pediatric ADEM patients with and without MOG-abs. The study pointed that it is not possible to distinguish ADEM patients with MOG-abs from those without it at the onset of disease, without testing for MOG- abs, based on a few clinical and radiological differences [14].

Serum MOG-abs were detected in our patient in the acute phase with a titer of 1:320. Based on the fact that the disappearance of the MOG-abs after the initial attack might have prognostic implication, we retested the serum MOG-abs in our patient after treatment with steroids. Serum MOG-abs were consistent with a titer of 1:320 at two-month review. There is no recommendation for regular monitoring of MOG-abs titers for relapse prediction as the literature review showed that only sparse data are available on the usefulness of regular monitoring of antibody titers in individual patients known to be positive for MOG-abs. No long-term data were provided for the most of reported monophasic MOG-abs positive ADEM children. Recent studies revealed a seroconversion in a few patients with relapsing disease as well as falling the titers bellow cut-off temporarily following treatment with steroids and rising again at a later disease stage [15, 16]. Acute treatment with corticosteroids is the current standard of care for MOGAD. Although initial event can be severe at presentation, acute treatment with intravenous methylprednisolone followed by slow oral prednisone taper showed excellent response with full recovery in most children. Intravenous immunoglobulins and plasmapheresis constitute second-line therapies in case of insufficient response to intravenous corticosteroids [17, 18]. Our patient was treated with intravenous methylprednisolone (20 mg / kg / 24 h) during five days followed by oral prednisolone (2 mg/kg) weaning course over eight weeks. During glucocorticoid therapy she made a gradual clinical improvement and at two-month review she recovered almost completely.

In conclusion, our case emphasizes the inclusion of the MOG-abs testing in the initial work-up in children presenting with acute encephalopathy associated with demyelinating or encephalitic abnormalities on brain and/or spinal MRI even when the clinical phenotype is unusual. The prompt diagnosis of MOGAD is relevant for accurate disease monitoring, treatment strategies and counselling of parents.

Conflict of interest: None declared.

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Приказ дечјег акутног дисеминованог енцефаломијелитиса удруженог са антителима према мијелинском олигодендроцитном гликопротеину

Татјана Рељек-Мудринић[1,2], Ивана Кавечан[1,2], Катарина Копрившек[1,2], Горан Ракић[1,2], Јасмина Пајић[2]

[1]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[2]Институт за здравствену заштиту деце и омладине Војводине, Нови Сад, Србија

САЖЕТАК

Увод Стања удружена са антителима према мијелинском олигодендроцитном гликопротеину су имунски посредоване запаљенске болести централног нервног система са различитом фенотипском варијабилношћу. Ради бољег разумевања могућих клиничких презентација, приказујемо педијатријски случај акутног дисеминованог енцефаломијелитиса удруженог са антителима према мијелинском олигодендроцитном протеину (МОГ антитела).

Приказ болесника Претходно здраво женско одојче узраста четири месеца је дан пред преглед имало повишену телесну температуру до 39°C уз повраћање. На пријему је било сомнолентно до сопорозно. Опсервирани су стереотипни репетитивни дистонични покрети горњих екстремитета. Преглед цереброспиналне течности је регистровао плеоцитозу (са предоминацијом лимфоцита) и протеинорахију. Серумска МОГ антитела су била позитивна. Продужена електроенцефалографија је регистровала ирегуларну, спороталасну електрокортикалну дисфункцију. Епилептиформне промене нису забележене током опсервираних симетричних дистоних покрета руку. На основу налаза магнетне резонанце постављена је дијагноза акутног дисеминованог енцефаломијелитиса. Болесник није имао конвулзивне нападе и поред постојања кортикалних лезија. Промптна кортикостероидна терапија је довела до потпуног неуролошког опоравка.

Закључак Овај случај наглашава значај испитивања МОГ антитела код деце која су развила знакове енцефалопатије са регистрованим лезијама централног нервног система, чак и када клиничка презентација није типична. Рано постављање дијагнозе је кључно за адекватно лечење и праћење тока болести.

Кључне речи: МОГ антитела; акутни дисеминовани енцефаломијелитис; дете; дистонија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A rare complication in a child undergoing chemotherapy for Hodgkin lymphoma – multiple cerebral venous sinus thrombosis

Aleksandar Kostić[1], Danijela Jovančić-Petković[2], Aleksandra Aracki-Trenkić[3], Nebojša Stojanović[1], Vesna Nikolov[1]

[1]Niš Clinical Center, Clinic for Neurosurgery, Niš, Serbia;
[2]Niš Clinical Center, Clinic for Pediatrics, Niš, Serbia;
[3]Niš Clinical Center, Center for Radiology, Niš, Serbia

SUMMARY
Introduction Risk factors for thrombotic events in patients receiving treatment for Hodgkin lymphoma are not well known. Administration of some cytostatic medication, especially via central venous catheter, corticosteroids, and hyperlipidemia can present some of them.
Case outline A case of a 15-year-old boy that had been newly diagnosed with Hodgkin lymphoma is presented here. Chemotherapy according to vincristine, etoposide, prednisone, and doxorubicin (OEPA) protocol was introduced a month before headache and vomiting occurred, so subsequently, brain computer tomography was performed, and reviled laminar subdural pseudo-hemorrhage in the right occipital region. After performing magnetic resonance imaging (MRI) venous thrombosis of the posterior part of superior sagittal sinus, right transverses, and sigmoid sinus were presented. Low-molecular-weight heparin (LMWH) and anti-edematous therapy was immediately initiated. Two weeks later, the patient resumed the second cycle of chemotherapy combined with LMWH, as the previous symptoms of intracranial hypertension resolved. Two years later, MRI showed an almost complete resolution of the finding. The boy was in good clinical condition.
Conclusion Although administration of oral corticosteroids, could be rarely a risk factor *per se* for cerebral sinus venous thrombosis in Hodgkin lymphoma patients, it remains an important treatment option. Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as the prevention of possible intracranial hypertension and even fatal outcome.
Keywords: Hodgkin lymphoma; chemotherapy; cerebral venous sinus thrombosis

INTRODUCTION

A French clinician Ribes [1] has published the first case of thrombosis of the sagittal sinus in a man who had suffered from altered conciseness and epilepsy, nearly two centuries ago. Recently, many facts considering pathogenesis, cause, and risk factors emerged, and novel diagnostic procedures and therapy options evolved. Risk factors associated with cerebral sinus venous thrombosis are proved to be inherited or acquired. The most frequently associated risk factor is congenital thrombophilia. If acquired, risk factors are numerous, like brain trauma [2], infections of the central nervous system [3] or local infections [4], nephrotic syndrome [5], cranial tumors [6], hematological conditions [7], medicaments and cranial surgery, pregnancy and puerperium [8].

Although we found a case of a girl that had cerebral venous thrombosis (CVT) in non-Hodgkin lymphoma [9], while reviewing the literature we could not find a description of Hodgkin lymphoma (HL) in children complicated specifically by cerebral sinus venous thrombosis [10]. This case report could be the first one published.

CASE REPORT

A 15-year-old boy was diagnosed with HL, *sclerosis nodularis CS IIIA,* two months before admission to the Clinic for Neurosurgery. The chemotherapy according to vincristine, etoposide, prednisone, and doxorubicin (OEPA) protocol was introduced and the patient tolerated it well. The dose for vincristine was 1.5 mg/m^2 IV on day 1, 8, and 15; for etoposide 125 mg/m^2 IV days 1–5; for prednisone 60 mg/m^2, *per os* days 1–15; and for doxorubicin 40 mg/m^2 IV, days 1 and 15 [11]. After the second cycle of the therapy, severe headache and vomiting occurred. Immediately, brain computer tomography was done (Figure 1) and a radiologist described laminar occipital subdural bleeding, so the patient was referred from the local medical center to a neurosurgical examination.

After admission, conservative therapy was introduced – 20% mannitol 60 ml/12h as anti-edematous therapy, and 500 mg of paracetamol when needed, as well as 5 mg of diazepam every evening. His initial white blood cell count was 0.5 × 10^9/L, neutrophils 0.04 × 10^9/L, lymphocytes 0.37 × 10^9/L, monocytes 0.02 × 10^9/L, and thrombocytes 158 × 10^9/L. After this, brain

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Correspondence to:
Aleksandar KOSTIĆ
Mirisnih vrba 10
18000 Niš, Serbia
aleko018@yahoo.co.uk

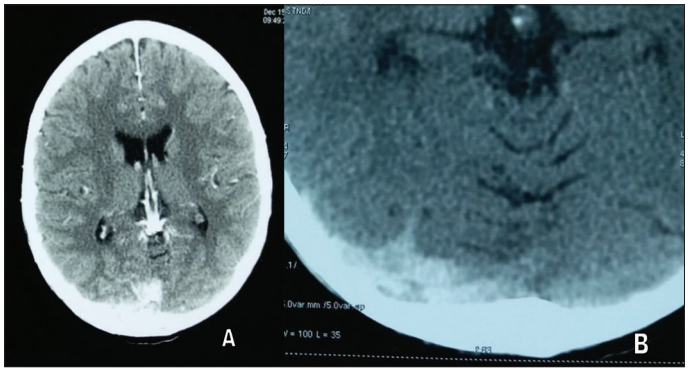

Figure 1. Initial computed tomography of the brain of a 15-year-old boy with sudden headache and vomiting; A: axial scan shows right occipital hyperdense area; B: enlarged axial scan presenting altered signal in the area of the right transverse sinus

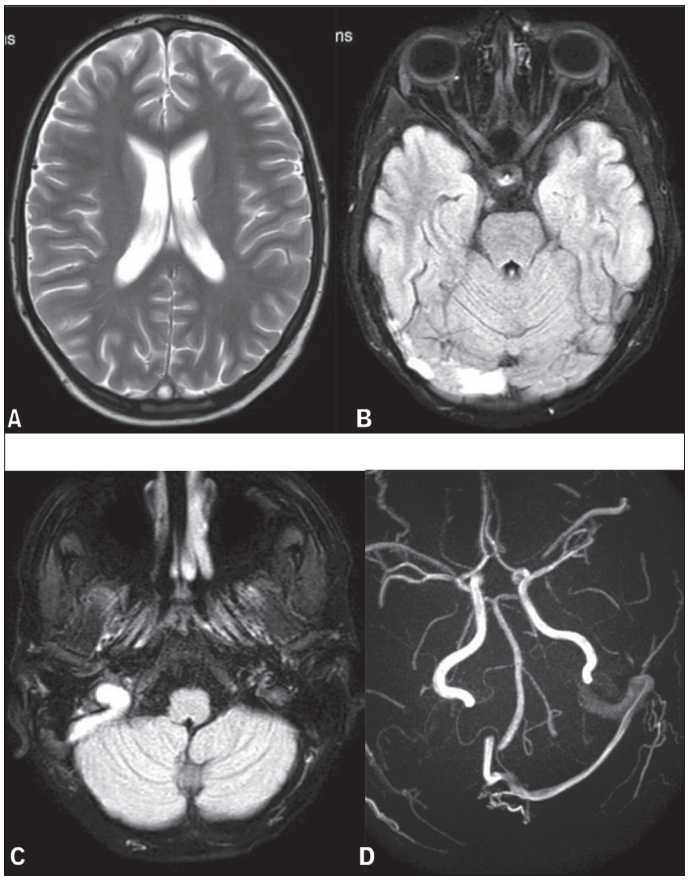

Figure 2. Brain MRI; A: axial T2W tomogram shows the "empty-delta" sign; B and C: axial FLAIR tomograms show thrombosis right transverse sinus (RTS) and right sigmoid sinus (RSS); D: MR angiogram presents thrombosis of the superior sagittal sinus, RTS, and RSS

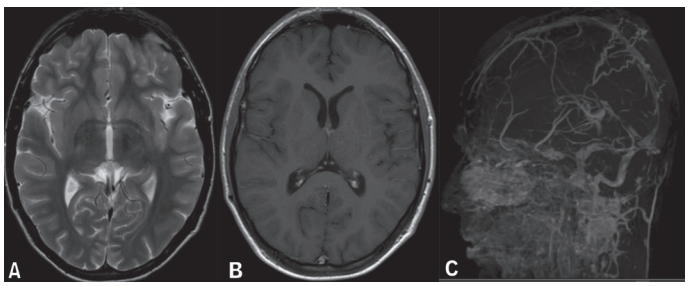

Figure 3. A: T2W axial tomogram presents recanalization of the superior sagittal sinus (SSS) (no delta sign); B: T1W postcontrast axial tomogram presents recanalization of the SSS; C: 3D magnetic resonance venography sinus recanalization

magnetic resonance imaging (MRI) and angio-MRI were performed and revealed not a hemorrhage but thrombosis of the superior sagittal sinus (SSS) (Figure 2A), right transverse (RTS), (Figure 2B), and sigmoid venous sinus (RSS) (Figure 2C). Foci of filling defect in the lumen of the sinuses with "empty-delta" sign on T2-weighted images appeared, but no signs of cerebral ischemia (Figure 2A).

The patient's coagulation status appeared to be normal, international normalized ratio (INR) of 1.3, prothrombin time (PT) of 26 seconds, partial thromboplastin time (PTT) of 75% were also in the normal range. Another MRI was performed 10 days later and no changes in findings were observed. Coagulation profile on the next day was as follows: PT 15 seconds, activated PTT 40.7 seconds, D-dimer 2.1 μg/mL, fibrinogen 241 mg/dL, cholesterol 140 mg/dL, and triglycerides (TG) 122 mg/dL. The eye exam showed a normal finding of the fundus. Low-molecular-weight heparin (LMWH), Fraxiparine® (Glaxo Wellcome Production, Notre Dame de Bondeville, France) was also administered subcutaneously in a dose of 2 × 0.6 ml per day. Several episodes of headache appeared again during the disease, and the patient was treated three to four days with mannitol 60 ml/12h, paracetamol, and 5mg of diazepam in the evening as antiseizure prevention.

The patient was not genetically tested. There were not any data about malignancies or blood diseases in family history. The levels of antithrombin, proteins C and S were normal, as well as the reaction of factor V to activated protein C.

After three weeks, the patient was discharged from hospital in good clinical condition and LMWH were administrated during the following six months. His INR values were 2.3–3.1. After LMWH, oral anticoagulant therapy rivaroxaban (Xarelto, Bayer AG, Leverkusen, Germany) 15 mg a day was administered for a few months. After that, antiplatelet therapy, acetylsalicylic acid (Cardiopirin, G.L. Pharma GmbH, Lannach, Austria) 100mg has been administrated up to the present day. A follow-up examination of brain MRI after six and 12 months revealed the partial resolution of thrombosis. There were no clinical symptoms or signs related to thrombosis. Two years later, control brain MRI (Figure 3) showed a complete resolution of the previous finding – minor residua of thrombosis. The boy was in a good clinical condition.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient's parent/guardian for the publication of this case report and any accompanying images.

DISCUSSION

HL is a lymphoid neoplasm, usually presented with specific histopathologic and clinic characteristics. Neurologic complications of HL are due to the disease itself or can be iatrogenic. Headache is the most common clinical manifestation in 89%, followed by focal deficit and epilepsy in one-half and one-third of the cases, respectively [12]. The first-choice diagnostic procedures are MRI and MR venography, while LMWH is a cornerstone of the treatment worldwide [12].

Why did the patient develop the CVST? Administration of L-asparaginase, dyslipidemia, and high body mass index in a child with acute lymphoblast leukemia (ALL) can cause SSS thrombosis. Hyperlipidemia is known to be one of the risk factors for cerebral venous sinus thrombosis, and L-asparaginase, a major component in effective ALL treatment, is highly associated with temporal hypertriglyceridemia in the pediatric population [13]. Corticosteroids alone can induce the activity of lipoprotein lipase, which may prevent a rise in TG on corticosteroid therapy [14]. On the other hand, some experimental studies showed that levels of clotting factors and fibrinogen are rapidly increased by glucocorticoids [15, 16]. In the population-based case–control study by Johannesdottir et al. [17], patients on corticosteroids had an increased risk of venous thromboembolism (VTE) and the effect was the strongest for new users of systemic glucocorticoids. Also, an interesting finding was that oral glucocorticoids were associated with a higher risk than the injectable form. They affect tissue factor-mediated leukocyte procoagulant activity and inhibit platelet aggregation in a later phase of treatment, and, in general, may not be the only reason for hypercoagulability in our patient. Chemotherapy for HL may lead to cerebral infarction on the basis of embolism due to cardiomyopathy. Anthracycline may induce cardiomyopathy [18].

Our patient was not treated with either of the abovementioned cytostatic, but according to the OEPA protocol, and a large cohort of 66,329 cancer patients with any malignancy, chemotherapy-treated patients had double increased risk of VTE compared to those who had not received chemotherapy [19]. In our case report, the patient also received oral prednisone 60 mg/m^2 for 15 days, and that could be the reason for developing CVST in addition to chemotherapy. He had a normal body mass index, and there were no laboratory findings of dyslipidemia, and his coagulation status appeared to be normal. Also, we did not perform genetic tests for congenital thrombophilia and that is a significant shortcoming of the report [20].

Administration of the cytostatic via a central venous catheter (CVC) is also a significant risk factor for developing VTE. David et al. [21] observed that 36% of NHL patients with catheters, regardless of therapy, experienced VTE events. Our institutional practice has been to administer OEPA via peripheral IV unless there was another indication for central access. In this particular case, the boy received therapy via a peripheral vein. Nonetheless, CVC-related thrombosis are not located in the brain. High-grade non-Hodgkin lymphoma is associated with the highest incidence rate of VTE (8.3%), followed by low-grade non-Hodgkin lymphoma and HL, 6.3%, and 4.7%, respectively [22].

Risk factors for thrombotic events in patients receiving treatment for HL are not well known. The largest and most comprehensive analysis of thrombotic events in HL patients is a study by Borchmann et al [23]. A total of 193 thrombotic events occurred for an incidence of 3.3%; 5773 HL patients and advanced-stage patients were at a higher risk for VTE. Prophylactic anticoagulant treatment is not warranted even for higher-stage HL patients, as long as they remain mobile or are without a history of a previous thrombosis [23]. The most frequent location of thrombosis in HL patients are upper and lower extremities and lungs [24]. The most common location sites for CVT, in the general population, are transverse sinus (86%), superior sagittal sinus (62%), straight sinus (18%), cortical veins (17%), jugular veins (12%), the vein of Galen and internal brain veins (11%) [25].

Starting from the middle of the 20th century, when CVT was considered a fatal illness, up to the MRI era, many series have shown a steady decrease in mortality. In recent studies, reported mortality rate in the acute phase was 4.3%, and 3.4% in evolution after 30 days [26]. Factors of poor prognosis are male sex, age over 37 years, altered consciousness, deep CVT, papilledema, and Glasgow Coma Scale score < 9 [27].

Adequate and prompt diagnostics and therapy are mandatory in cases of wide intracranial venous thrombosis as a prevention of possible intracranial hypertension and even fatal outcome. Although administration of oral corticosteroids could be rarely a risk factor *per se* for cerebral sinus venous thrombosis in HL patients, it remains an important treatment option.

Conflict of interest: None declared.

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Ретка компликација код детета током хемотерапије Хоџкиновог лимфома – вишеструке тромбозе церебралних венских синуса

Александар Костић[1], Данијела Јованчић-Петковић[2], Александра Арацки-Ренкић[3], Небојша Стојановић[1], Весна Николов[1]

[1]Клинички центар Ниш, Клиника за неурохирургију, Ниш, Србија
[2]Клинички центар Ниш, Клиника за дечју интерну медицину, Ниш, Србија;
[3]Клинички центар Ниш, Центар за радиологију, Ниш, Србија

САЖЕТАК

Увод Фактори ризика настанка тромбозе болесника лечених од Хоџкиновог лимфома нису до краја разјашњени. Примена неких цитостатика, нарочито преко централне венске линије, кортикостероди и хиперлипидемија могу бити неки од њих.

Приказ болесника У раду је приказан случај дечака, 15-годишњака, коме је постављена дијагноза Хоџкиновог лимфома. Према терапијском протоколу винкристина, етопозида, преднизона и доксирубицина (ОЕПА) ординирана је хемиотерапија месец дана пре појаве главобоље и повраћања, па је урађена компјутеризована томографија мозга и показала је постојање танког псеудосубдуралног хематома у пределу десног окципиталног режња. Након урађене магнетне резонанце мозга заправо је откривена тромбоза горњег сагиталног синуса, десног транзверзалног и сигмоидног венског синуса. Ординирани су нискомолекуларни хепарин и антиедематозна терапија. После две недеље болеснику је укључен други циклус хемиотерапије у комбинацији са нискомолекуларним хепарином, пошто су се знаци интракранијалне хипертензије повукли. После две године налаз магнетне резонанце мозга показао је готово потпуну нормализацију стања. Дечак је био у добром клиничком стању.

Закључак Иако примена оралних кортикостероида може повремено бити фактор ризика за развој церебралних тромбоза венских синуса код болесника са Хоџкиновим лимфомом, они остају као незаобилазан вид третмана. Адекватна и брза дијагноза и терапија су обавезне у случајевима са раширеном венском тромбозом, а ради превенције интракранијалне хипертензије и последичног смртног исхода.

Кључне речи: Хоџкинов лимфом; хемотерапија; тромбоза венског церебралног синуса

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Combined laparoscopic-endoscopic "rendez-vous" procedure in a case of gastric schwannoma in a toddler

Radoica Jokić[1,2], Slaviša M. Đuričić[3,4], Jelena Antić[1,2], Ivana Fratrić[1,2]

[1]Institute for Child and Youth Healthcare of Vojvodina, Clinic for Pediatric Surgery, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia, Department of Clinical Pathology, Belgrade, Serbia;
[4]Banja Luka University, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction Schwannomas are rare benign tumors of the gastrointestinal tract. Despite the differences in features of schwannomas located in the stomach as opposed to peripheral or soft tissue schwannomas, their immunohistochemical characteristics are the same. We present a case of a 14-month-old boy with a gastric tumor who underwent a combined laparoscopic-endoscopic resection surgery, followed by gastric schwannoma diagnosis.

Case outline The patient was admitted to our pediatric hospital with a fever of unknown origin. Endoscopy, performed after recurrent hematemesis, revealed an ulcer in the gastric antrum. At the four-week follow-up, gastroscopic and microscopic findings were normal. Two weeks later, a flank mass in the antrum was detected by an ultrasound examination. A new gastroscopy and CT scan confirmed the presence of a tumor-like mass, 5 cm in diameter. A combined laparoscopic-endoscopic polypectomy was performed with a necessary conversion for complete resection of tumor. The initial histological findings were consistent with a gastrointestinal stromal tumor. Due to this tumor's rarity in childhood, the paraffin-embedded tissue samples were referred for a second opinion. Histological and immunohistochemical characteristics of the tumor made the gastrointestinal stromal tumor diagnosis unlikely and consistent with a completely resected gastric schwannoma. No recurrence of the disease occurred during the seven-year follow-up.

Conclusion Combined laparoscopic-endoscopic surgery is a feasible and effective treatment for large gastric tumors that cannot be excised endoscopically. Schwannoma should be included in the differential diagnostic consideration of gastric tumor lesions even in childhood.

Keywords: stomach; laparoscopy; endoscopy; neurilemmoma

INTRODUCTION

Gastrointestinal (GI) schwannoma was first described in 1988 by Daimaru et al. [1]. The stomach is the most common site, and gastric schwannoma (GS) represents 0.2 % of all gastric neoplasms [2]. They are believed to arise from the disperse autonomic nerve Schwann cells, in contrast to much more common schwannoma of the skin, connective tissue, and other internal organs that arise from peripheral nerves. These differences are also related to schwannomas' gross and histological features in the gastric location [2]. Also, unlike peripheral schwannoma, GS is rarely associated with neurofibromatosis, so it probably has a different genetic basis [3, 4, 5]. However, the immunohistochemical characteristics of schwannomas in all locations are the same. Immunohistochemistry plays a pivotal role in distinguishing GSs from more common mesenchymal tumors in the GI tract: gastrointestinal stromal tumor (GIST), smooth muscle neoplasms and inflammatory fibroid polyp [2–5].

GS occurs predominately in adults and is more common in women. The symptoms are nonspecific and it may be detected incidentally [2, 4, 6].

Endoscopy with simultaneous resection of the lesion is highly advisable for GI lesions in mucosal and submucosal locations. Still, open or laparoscopic surgical resection has been the only available treatment in most cases of deeply sited gastric neoplasms with excellent postoperative prognosis [2, 4, 7, 8].

We present a case of a 14-month-old boy with a gastric tumor who underwent a combined laparoscopic-endoscopic resection procedure, followed by the histopathological diagnosis of GS.

CASE REPORT

The patient was admitted to our pediatric clinic with a fever of unknown origin. Clinical examination did not reveal the cause of the fever. Non-steroidal anti-inflammatory drugs were administered. After recurrent hematemesis, on the seventh day of the hospitalization, endoscopy was performed, which revealed a large ulcer with a diameter of 38 mm in the stomach's

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Correspondence to:
Radoica JOKIĆ
Hajduk Veljkova 10
21000 Novi Sad, Serbia
radoica.jokic@mf.uns.ac.rs

antropyloric segment (Figure 1A). Afterwards, the patient was under a clinical follow-up and was treated with pantoprazole. After a four-week follow-up, gastroscopic and microscopic findings were normal (Figure 1B). Two weeks later, a flank mass in the antrum was found by an ultrasound examination. New gastroscopy and CT scan confirmed the presence of a well circumscribed, polypoid, submucosal tumor mass measuring 4.8 × 4 × 4 cm, lined with flattened mucosa, in the antropyloric region.

A combined laparoscopic-endoscopic resection, the so-called "rendez-vous" procedure, was performed the next day. Under general anesthesia, the endoscope was inserted, and the location and diameter of the tumor was confirmed (Figure 1C). Then the camera port was inserted in a standard infraumbilical position using an open Hasson technique. A carbon dioxide pneumoperitoneum was established, with a pressure of 8–10 mmHg. Two additional ports (5 mm) were inserted into the left and right upper quadrants. Firstly, a front abdominal wall gastrotomy was performed using endoscopy navigation. Then an excision of the tumor in its entirety was made. The standard laparoscopic operation was practically converted to video-assisted procedure (Figure 1D). It means that the stomach was exteriorized through umbilical port, which was slightly enlarged, and polypectomy was performed extracorporeally. As a result, the defect remained on the back wall due to the radicality of the resection. The operation was completed with the closure of the posterior and anterior stomach wall, both with direct sutures. Finally, a nasogastric tube was placed.

Initially, the tumor, which measured 5 cm in the largest diameter (Figure 1E), was diagnosed as GIST. Due to the extreme rarity of GIST in childhood, tissue samples were sent for a second opinion (Belgrade). The tumor was composed of elongated spindle cells with mild nuclear atypia and moderate mitotic activity (15 mitoses / 50 high-power field). Interstitium was myxomatous with a decreased density of tumor cells. Except in the central area of the ulceration, the tumor was lined with atrophic mucosa. The tumor at the base showed infiltrative growth between the muscle propria fibres (Figure 2A–C). After immunohistochemical staining, tumor cells were positive for vimentin, S-100 (Figure 2D), GFAP, focally CD34, and negative for desmin, muscle-specific and smooth muscle actin, caldesmon, calponin, CD117, DOG1, ALK-1, CK, EMA, BCL-2, CD99, and TLE-1. Histological and immunohistochemical characteristics of the tumor made the diagnosis of GIST extremely unlikely and were consistent with GS. Resection margins were tumor-free. Histological and immunohistochemical analyses were repeated by an expert team (Liverpool, UK), who agreed with the diagnosis of GS. Due to the lack of clinical criteria and negative family history, neurofibromatosis was also unlikely.

The postoperative course was uneventful. No adjuvant therapy was administered. There was no recurrence of the tumor during seven years of follow-up (Figure 1F).

This study was designed as a case report and was conducted according to the guidelines of the Declaration of Helsinki. It was approved by the Institutional Review Board of the Institute for Child and Youth Healthcare of Vojvodina (No 2284 from June 4, 2021).

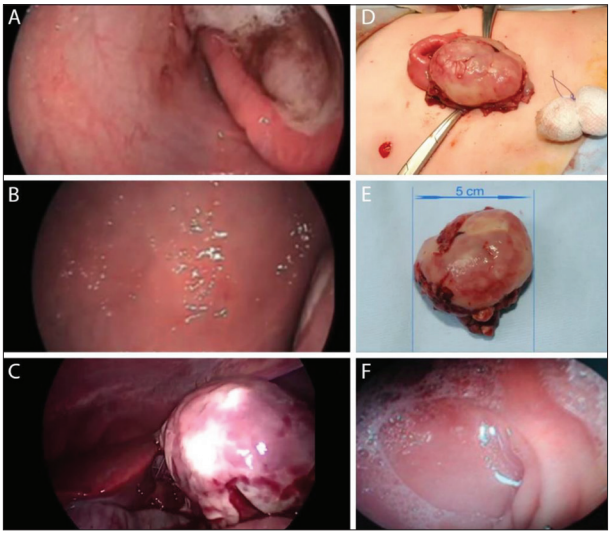

Figure 1. Diagnostic and treatment procedures; A: a large ulcer in the gastric antrum found on the first endoscopy; B: a normal finding on the second endoscopy; C: laparoscopic view of the tumor after opening the anterior wall of the stomach; D: conversion to video-assisted surgery; E: macroscopic appearance of the tumor; F: postoperative endoscopy

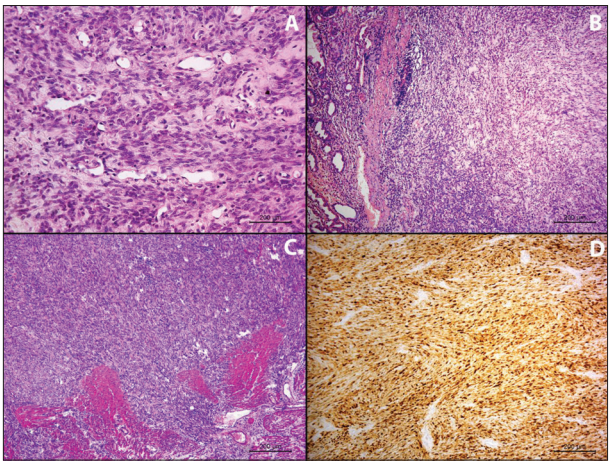

Figure 2. Histology of the gastric schwannoma; A: microtrabecular growth pattern of relatively uniform spindle cells and dilated capillaries in the stroma (H&E, × 200); B: atrophic gastric mucosa above the tumor (H&E, × 100); C: infiltrative growth through the muscularis propria at the base of the tumor node (H&E, × 50); D: immunohistochemically typical diffuse tumor cells positivity for S-100 protein (× 100)

DISSCUSION

Most tumors located in the stomach above the muscularis propria can be excised endoscopically. The available techniques comprise snare polypectomy, endoscopic mucosal resection (EMR), and piecemeal EMR [9, 10]. If the tumor is located in the deeper layers, the possibility of complete resection is questionable. The optimal treatment for such tumors is an open or laparoscopic surgery [11, 12].

Laparoscopic wedge resection is being performed with increasing frequency [13, 14, 15]. In 2004, the National

Comprehensive Cancer Network and The European Society of Medical Oncology published consensus statements doubting the efficacy of laparoscopic resection for GIST of the stomach [16]. In this report, laparoscopic resection is approved for GIST smaller than 2 cm. According to recent publications, many surgeons achieved complete resection (R_0) laparoscopically, with no complications in terms of rupture or tumor spillage [17].

Combined laparoscopic-endoscopic techniques represent an innovative concept in the treatment of colonic and gastric lesions. The idea for this approach came from the paper by Pelizzo et al. [18] published in 2007. The first procedure in our clinic was performed 13 years ago to treat a patient with familial adenomatous polyposis syndrome. Minimally invasive "rendez-vous" surgery allows for the opportunity to make an accurate histological analysis while a high level of patient comfort is maintained [19, 20].

About three-quarters of GI tract schwannomas are located in the stomach, most commonly in the area of the great curvature, followed by antrum and fundus [4, 5, 6, 8]. Lauricella et al. [8] found 686 patients with GS published in the English-language literature over a period of 30 years. Most of the articles dealt with individual cases. Only 10% of all tumors were removed endoscopically, while an equal number of other tumors were removed by total/subtotal gastrectomy and local excision, respectively. Tumor recurrence was very infrequent and did not depend on the surgical method.

All of 221 patients with GS in the literature review by Hu et al. [6] were older than 40 years. The youngest registered patient with GS so far was a 16-year-old girl [21].

The histological features of the tumor in our patient confirm that GS histologically differs somewhat from peripheral or soft tissue schwannoma. Unlike soft tissue schwannoma, GS is usually not encapsulated, lacks nuclear palisading (Verocay bodies), alternating areas of hypercellularity (Anthony A and B), vascular hyalinization and dilatation. GS often has a peritumoral cuff-like lymphocytic infiltration, microtrabecular architecture and cellular atypia [4, 6]. Mitotic activity in our tumor was at the upper limit (criteria for separating benign from malignant GS) [6]. GS is very rarely associated with neurofibromatosis 1 and 2 syndrome.

Immunohistochemical analysis remains the main diagnostic method for distinguishing spindle cell tumors, including mesenchymal tumors of the gastric wall. In our case, repeated analyses in two laboratories specialized in pediatric pathology showed negative immunohistochemical staining results with markers characteristically positive in GIST (CD117, DOG1). The key markers for schwannoma differentiation, S-100 and GFAP, were positive in this case. Also, the immunophenotype of tumor cells did not correspond to some of the very rare childhood tumors (myofibroblastic neoplasms, solid fibrous tumor, synovial sarcomas, and some types of hemangioendotheliomas).

Combined laparoscopic-endoscopic polypectomy is a feasible and effective treatment for large gastric tumors that cannot be excised endoscopically. This is a safe technique that enriches the therapeutic range of the surgeon and healthcare institution in which it is performed. This case suggests that schwannoma should be included in the differential diagnostic consideration of gastric tumor lesions even in childhood.

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Комбинована лапароскопско-ендоскопска „рандеву" процедура у случају гастричног шванома код малог детета

Радоица Јокић[1,2], Славиша М. Ђуричић[3,4], Јелена Антић[1,2], Ивана Фратрић[1,2]

[1]Институт за здравствену заштиту деце и омладине Војводине, Клиника за дечју хирургију, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Институт за здравствену заштиту мајке и детета Србије „Др Вукан Чупић", Одељење за патологију, Београд, Србија;
[4]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод Шваноми су ретки бенигни тумори гастроинтестиналног тракта. Без обзира на разлике у особинама шванома желуца и шванома периферних нерава, њихове имунохистолошке карактеристике су исте. Представљамо четрнаестомесечно дете са гастричним тумором који је ресециран комбинованом лапароскопско-ендоскопском техником, након чега је постављена дијагноза гастричног шванома.

Приказ болесника Болесник је примљен на нашу педијатријску клинику због фебрилности непознатог узрока. Након понављаних хематемеза, током ендоскопије откривен је улкус у антруму желуца. Након четири недеље, резултати гастроскопије и микроскопске анализе били су уредни. Две недеље касније, током ултрасонографског прегледа виђена је полипоидна формација у пределу антрума. Поновљена гастроскопија и КТ потврдили су присуство туморске масе пречника 5 *cm*. Урађена је комбинована лапароскопско-ендоскопска полипектомија са неопходном конверзијом у циљу комплетне ресекције тумора. Иницијални хистолошки резултат указивао је на гастроинтестинални стромални тумор. Због реткости овог тумора у дечјем узрасту, послате су парафинске плочице ради добијања другог мишљења. На основу хистолошке и имунохистохемијске анализе у лабораторијама педијатријске патологије утврђено је да се ради о гастричном шваному, који је у целини одстрањен. Није било рецидива болести током седмогодишњег праћења болесника.

Закључак Комбинована лапароскопско-ендоскопска ресекција могућа је и ефикасна терапија за лечење туморских лезија у зиду желуца које се не могу одстранити ендоскопски. Шваном је неопходно укључити у диференцијалнодијагностичка разматрања туморских лезија желуца, чак и у дечјем узрасту.

Кључне речи: желудац; лапароскопија; ендоскопија; неурилемом

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Mature ovarian teratoma-associated encephalitis

Anita Krsman[1,2], Branislava Baturan[1,2], Dmitar Vlahović[3], Zorica Grujić[1,2], Đorđe Petrović[1,2], Biljana Radovanović[3]

[1]Clinical Center of Vojvodina, Department of Obstetrics and Gynecology, Novi Sad, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Clinical Center of Vojvodina, Department of Neurology, Novi Sad, Serbia

SUMMARY

Introduction Autoimmune encephalitis associated with ovarian teratoma is a serious and potentially fatal pathology. While this clinical entity is known to neurologists, the available literature rarely mentions the role of a gynecologist in diagnostic imagining and treatment. Although several months have passed from the onset of symptoms to surgical treatment, this case shows that even then a complete recovery is possible.

Case presentation The patient was a 28-year-old female, brought to the hospital because a sudden onset of unusual behavior – an acute psychosis with suicidal thoughts and auditory hallucinations. Soon after the admission she became delirious, uncooperative and agitated. Blood check, neurological assessment and cranial computed tomography yielded normal results. Therefore, a psychiatric disorder was suspected. Electroencephalogram revealed a diffuse encephalitic insufficiency. As cerebrospinal fluid was negative for infections, the autoimmune etiology of the disease was suspected. Abdominal computer tomography showed a complex right ovarian mass measuring 50 × 40 × 30 mm, confirmed by vaginal ultrasound. Laparoscopy with right adnexectomy was performed. The pathohistological finding showed a mature teratoma. In the meantime, the result of the cerebrospinal fluid test came positive for Anti-N-Methyl-D-Aspartate antibodies. Six months after surgery, the patient was in a good mental and neurological status without symptoms.

Conclusion Gynecologists should be aware of the presence of ovarian tumors in encephalitis cases. A timely diagnosis of the underlying gynecological cause of a neurological condition, allows for prompt treatment and can remarkably improve clinical conditions and, thus, be lifesaving.

Keywords: autoimmune encephalitis; teratoma; tumor; young women

INTRODUCTION

Anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis has been recognized as the second most common cause of autoimmune encephalitis, after acute demyelinating encephalomyelitis [1]. Anti-NMDAR encephalitis in young women is usually associated with the presence of ovarian masses. [1, 2]. Due to the prevalence of psychiatric symptoms, 77% of patients are initially hospitalized by a psychiatrist [3, 4, 5]. The above symptoms are followed by a memory deficit, autonomic instability, seizures, muscle rigidity, movement disorder and hypoventilation [6]. It is not uncommon for such patients to require ventilation support and intensive care to stay alive [7]. In this patient, withdrawal symptoms and recovery occurred immediately after surgical treatment, although literature data show that recovery can take up to 24 months [1, 2, 7]. However, some patients still have problems with cognition (understanding, memory, attention and expression) and motor function (walking, taking care of yourself, swallowing) [1]. Anti-NMDAR encephalitis is well known to neurologist. Still, this is less well known to gynecologists, who may have a decisive role in etiological management. Raising awareness about this disease among gynecologists can be of great importance for earlier diagnosis and thus faster healing [8].

We present a rare case of Anti-NMDAR encephalitis induced by ovarian teratoma. Although five months passed from the appearance of the first symptoms to removal of the tumor, our patient completely recovered without consequences. The purpose of the study was to present our first experience, as gynecologists, with such a rare pathology and to point out the challenge in diagnosis and treatment patient with NMDAR encephalitis.

CASE REPORT

A 28-year-old woman was hospitalized at the Clinic for Psychiatry, Clinical Center of Vojvodina, complaining of symptoms of an acute episode of psychotic behavior. According to hetero-anamnestic data, the patient had a sudden onset of unusual behavior, an acute psychosis with suicidal thoughts, auditory hallucinations and decreased food intake. Soon after admission, she became delirious, uncooperative and agitated. She had no past medical history and there was no history of substance abuse. Fear, loss of appetite, decreased oral intake and insomnia were the dominant symptoms. The

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Correspondence to:
Anita KRSMAN
Department of Obstetrics and Gynecology
Clinical Centre of Vojvodina
Branimira Ćosića 37
Novi Sad
Serbia
anitaanaaleksic@gmail.com

neurological assessment and basic blood evaluation yielded negative results; cranial computed tomography (CT) was unremarkable. The patient exhibited severe psychomotor agitation, which led to self-inflicted harm. In the further course of hospitalization, she destroyed her lower lip and caused a fracture of the alveolar extension of the lower jaw. An extensive array of microbiological and serological tests were done, and all were negative. The autoimmune antibodies and tumor marker examination results were also negative. The brain magnetic resonance imaging (MRI) and angiography (MRA) were unremarkable. Electroencephalogram (EEG) revealed a diffuse encephalitic insufficiency. The sample of cerebrospinal fluid was negative for infections and was placed for further testing of anti-NMDAR antibodies. The patient was started on intravenous (IV) steroids, IV immunoglobulin (IVIG) and plasma exchange. There was a slight improvement after the applied therapy.

Finally, since autoimmune encephalitis (anti-NMDAR) is usually caused by the presence of a dermoid cyst in young women [1], a gynecologist was consulted. The CT showed the presence of a complex right ovarian mass measuring 50 × 40 × 20 mm, confirmed by vaginal ultrasound (Figures 1 and 2). Laparoscopy with right adnexectomy was performed. The ovarian mass contained cystic components as well as skin, hair, brain tissue and cartilage. The final pathology result was mature teratoma. In the meantime, the result of the cerebrospinal fluid test was positive for anti-NMDAR antibodies. After four months, the patient had problems with short-term memory. Six months after the surgery, the patient was in a good mental and neurological status, without any symptoms.

Written consent to write and publish this case report was obtained from the patient. The review was approved by the Ethics Committee of the Clinical Center of Vojvodina.

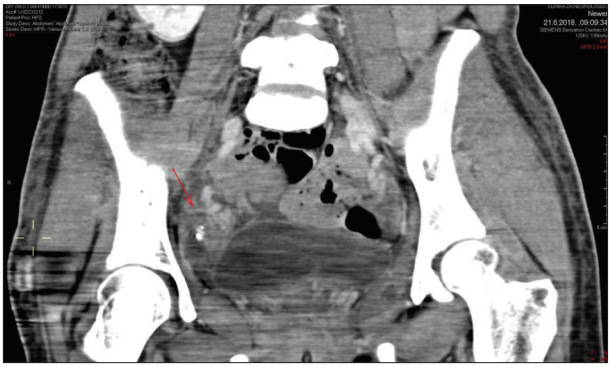

Figure 1. Computed tomography scan of the patient's pelvis

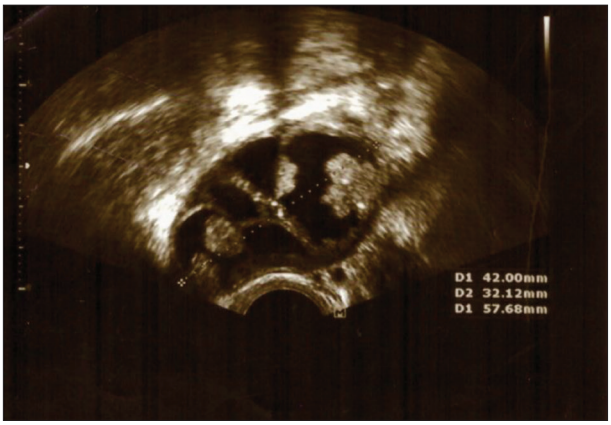

Figure 2. Transvaginal ultrasound of the ovarian teratoma in our patient

DISCUSSION

Teratoma-associated encephalitis (Anti-NMDAR encephalitis) was first noted in 1997 [1, 2, 9, 10]. Dalmau et al. [11] was the first to describe the progressive and potentially fatal course of this phenomenon. NMDA receptors are involved in cognitive processes: behavior, memory and learning [3]. Delay in diagnosis adversely affects the outcome which ranges from complete recovery, recovery followed by psycho–neurological sequelae, to death. An accurate and rapid diagnosis, followed by an early removal of the tumor in combination with immunotherapy, leads to a favorable outcome. This disease affects mostly young women and is associated with ovarian teratomas, which can contain nervous tissue expressing NMDA receptors [1, 2, 12]. However, cases have been reported in patients aged from eight months to 85 years [1]. Although there is a possibility of extra -ovarian teratomas (2%) and other tumors (4%, for instance lung, breast, thymus), ovarian teratomas are most often associated with this type of encephalitis [13]. Anti-NMDA receptor encephalitis often (70%) begins with prodromal flu-like symptoms (fever, headache and fatigue) [2]. After this uncharacteristic clinical picture, psychological symptoms develop with a predominance of the following: agitation, hallucinations, changes in behavior and anxiety [14]. There is a significant overlap of neurological and psychiatric symptoms associated with autoimmune encephalitis. Therefore, cases like this can manifest as a whole spectrum of neurological or psychiatric diseases (schizophrenia, paranoia, hallucinations, agitation, depression, anxiety, or substance abuse) [15]. The diagnosis of autoimmune encephalitis is challenging because the differential diagnosis involves the exclusion of the entire spectrum of the diseases (herpes simplex virus encephalitis, cytomegalovirus encephalitis, Hashimoto's encephalopathy, systemic lupus erythematosus encephalopathy, antiphospholipid antibody syndrome, Sjögren's syndrome, and primary central nervous angiitis). However, inadequate response to psychiatric therapy and neurological status should lead clinicians to consider encephalitis. MRI has been reported to be negative in up to 50–70% of cases, and in our case as well [15]. EEG abnormalities are present in most cases (90%) [1]. The final diagnosis is based on the presence of anti-NMDA autoantibodies in cerebrospinal fluid [2]. After anti-NMDA encephalitis has been confirmed, imaging studies are performed, such as vaginal ultrasound examination, MRI, CT and positron emission tomography [16, 17]. It is important to note that if autoimmune etiology is suspected it is necessary to intensively search for tumor changes in the ovaries [18]. Transvaginal ultrasound should be the first step in the

diagnosis of ovarian masses [2]. Therefore, gynecologists must be aware of the connection between ovarian tumors and autoimmune encephalitis and look in detail for even minimal ovarian changes. Sometimes this syndrome has been associated with patients without detectable underlying neoplasms. It is theorized that the syndrome may be triggered by microscopic germ cell tumors undetectable by imaging diagnostic methods [4]. Moreover, it has been reported that ovarian teratomas were discovered years after the onset of symptoms of anti-NMDAR encephalitis [4]. Surgical intervention is imperative, since a study by Titulaer MJ et al. [1] showed that five out of six patients with a confirmed NMDA encephalitis and an ovarian teratoma who did not undergo surgery died. The removal of the tumor will lead to an improvement in the patient's neurological performance within a few days or weeks [15]. The data from previous research indicate that a surgical procedure with immunotherapy have the best results in the treatment of this potentially fatal condition [2, 11]. Any delay in treatment can result in worsening of the patient's condition and even death [1]. It has been found that the outcome is more favorable if the operation is conducted after less than four months from the onset of symptoms [11]. In the case of this patient, the surgical treatment was performed 5.5 months after the appearance of the first symptoms. Women of the reproductive age are most often affected with this disease so the biggest challenge for gynecologists is how to completely remove the tumor while preserving fertility in the patient. Because a laparoscopic examination for determining ovarian teratoma is less-invasive than laparotomy, trial laparoscopy is acceptable if an ovarian tumor cannot be detected by various imaging tests [8]. Additionally, there have been cases where, despite the fact that the imaging procedures did not determine the existence of ovarian tumors, an ovariectomy was performed in order to stop the production of antibodies [3, 19, 20]. Postoperative histological examination in these cases confirmed the existence of occult teratoma consisting of skin, hair, cartilage and nervous tissue. Types of surgical treatment range from selective removal of lesions by ultrasound-guided laparoscopy, cystectomy, uni/bilateral ovariectomy and uni/bilateral adnexectomy [21]. Although some studies emphasize that cystectomy and adnexectomy have similar outcomes, we decided to perform a unilateral adnexectomy [22, 23]. As a possible limitation of the type of treatment in this case, we can mention the extent of the surgical procedure, which is not in accordance with the previous statements about preserving the fertility of young women. Pathohistological examination confirmed the existence of a mature teratoma with components of nervous tissue. This is consistent with literature reports showing that dermoid cysts, containing nervous tissue, are the most common pathohistological finding in patients with anti-NMDAR encephalitis [12].

As a limitation of the study, we state the period of postoperative monitoring. We followed the patients for six months postoperatively and it is not known whether the patient will develop new symptoms in the subsequent period. However, this case report may help identify this rare disease and therefore it is an important educational article.

In conclusion, it should be highlighted that it is extremely important to discover the cause of the disease as soon as possible, in order to give the patient the best chance of complete recovery. Since gynecologists play an important role in the treatment of these patients, they should be aware of the presence of tumors in patients with encephalitis. Determining the gynecological etiology of this condition, with the earliest possible surgical treatment, can lead to a favorable outcome and thus save the lives of young women.

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Зрели тератом јајника повезан са енцефалитисом

Анита Крсман[1,2], Бранислава Батуран[1,2], Дмитар Влаховић[3], Зорица Грујић[1,2], Ђорђе Петровић[1,2], Биљана Радовановић[3]

[1]Клинички центар Војводине, Клиника за гинекологију и акушерство, Нови Сад, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Нови Сад, Србија;
[3]Клинички центар Војводине, Клиника за неурологију, Нови Сад, Србија

САЖЕТАК

Увод Аутоимуни енцефалитис повезан са тератомом јајника је озбиљна и потенцијално фатална болест. Иако је ово познат клинички ентитет неуролозима, желели бисмо да скренемо пажњу гинеколозима, јер имају посебну улогу у дијагностици и оперативном лечењу болесница оболелих од аутоимуног енцефалитиса.

Приказан је случај болеснице чији је исход лечења успешан, иако је од појаве првих симптома па до постављања дијагнозе и операције прошло више месеци.

Приказ болесника Болесница стара 28 година хоспитализована је због изненадног развоја психозе са звучним халуцинацијама и суицидним мислима. Убрзо након пријема болесница постаје изразито узнемирена и агресивна. Лабораторијске анализе, неуролошки статус и компјутеризована томографија ендокранијума били су уредни. Електроенцефалограм је показао дифузни енцефалитис. Прегледом ликвора искључен је инфективни узрочник. Постављена је сумња на аутоимуну етиологију обољења. Компјутеризованом томографијом абдомена и вагиналним ултразвучним прегледом уочена је комплексна туморска промена десног јајника димензија 50 × 40 × 30 *mm*. Урађена је десна аднексектомија лапароскопски. Патохистолошка анализа је показала да се ради о зрелом тератому. Накнадно је пристигао позитиван узорак ликвора на анти-НМДА антитела. Шест месеци након операције болесница је уредног психичког и неуролошког статуса без тегоба.

Закључак Гинеколози треба да буду свесни постојања везе између енцефалитиса и тумора јајника младих жена. Брзо постављање дијагнозе, утврђивање гинеколошког узрока неуролошког обољења и адекватан терапијски поступак воде излечењу овог озбиљног, а понекад и смртоносног обољења.

Кључне речи: аутоимуни енцефалитис; тератом; тумор; младе жене

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Primary sarcomas of the larynx – a report of three cases and literature review

Aleksandar Ugrinović[1], Aleksandar Trivić[1,2], Vladimir Đorđević[1,2], Nada Tomanović[3], Miljan Folić[1,2]

[1]University Clinical Centre of Serbia, Clinic for Otorhinolaryngology and Maxillofacial Surgery, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Department of Otorhinolaryngology with Maxillofacial Surgery, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY

Introduction Primary sarcomas are uncommonly seen in the larynx and comprise around 1% of all laryngeal malignant tumors. We present three cases of patients with different types of laryngeal sarcomas and discuss about diagnostic and treatment difficulties.

Case outline Each patient presented with hoarseness and shortness of breath. Computed tomography scans showed large transglottic tumors of the larynx with no signs of cervical lymphadenopathy and definitive diagnoses of sarcomas were made by pathologists. Each patient underwent total laryngectomy with clear resection margins. Patient with laryngeal leiomyosarcoma developed large locoregional relapse of malignant disease and pulmonary metastasis four months after surgery and patient with laryngeal osteosarcoma was diagnosed with inoperative locoregional relapse of malignant disease three months after surgery. Both patients died within six months after surgery. On the other hand, patient with laryngeal chondrosarcoma was disease-free during the three-year follow-up.

Conclusion Primary laryngeal sarcomas have low incidence and they differ from squamous cell carcinoma by their biological characteristics and behavior. Radical surgical resection remains the mainstay of treatment with uncertain outcome due to their high potential for recurrence or metastatic spread.

Keywords: sarcoma; leiomyosarcoma; osteosarcoma; chondrosarcoma; laryngeal neoplasms; laryngectomy

INTRODUCTION

Squamous cell carcinoma (SCC) accounts for 95–98 % of laryngeal carcinoma. On the other hand, primary sarcomas are uncommonly seen in larynx and comprise around 1 % of all laryngeal malignant tumors [1]. Considering the low incidence of laryngeal sarcomas, most of the literature data are obtained from single case reports and scanty [2, 3, 4]. The fact that they differ a lot in their biological behavior from SCC is what makes the accurate diagnosis essential in their management.

We present three cases of patients with different types of laryngeal sarcomas and discuss about diagnostic and treatment difficulties.

CASE OF LARYNGEAL LEIOMYOSARCOMA

A 58-year-old male presented to our clinic with complaints of shortness of breath and hoarseness which had been ongoing for several months. The patient had a medical history of previous endoscopic laryngeal surgery due to vocal fold polyp. Also, the patient had been exposed to toxic substances for years while working in a paint and varnish production facility. Indirect laryngoscopy and microlaryngoscopy revealed large infiltrative laryngeal tumor of the right ventricular fold and both vocal folds with subglottic extension for 10 mm, which was seen also on computed tomography (CT) scan (Figure 1). The tumor paralyzed the right vocal fold and partially obstructed the airway. CT scan and neck ultrasonography showed no signs of cervical lymphadenopathy, and chest radiograph was normal. The diagnosis of low-grade laryngeal leiomyosarcoma (LLMS) was made after immunohistochemical analysis (Figure 2). The patient underwent total laryngectomy with clear resection margins (T3 tumor stage). He had a quick recovery and a successful voice rehabilitation. Unfortunately, the patient developed a large locoregional relapse of malignant disease and pulmonary metastasis four months following the surgery. Chemotherapy was not used due to pronounced bleeding from the tumor recurrence which caused the patient's death six months after laryngectomy.

CASE OF LARYNGEAL OSTEOSARCOMA

A 59-year-old male was admitted to hospital treatment due to severe dyspnea. Initial management was conducted as urgent tracheostomy and followed by CT scan and microlaryngoscopy, which point to a large, locally destructive

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Correspondence to:
Miljan FOLIĆ
University Clinical Centre of Serbia
Clinic for Otorhinolaryngology and Maxillofacial Surgery
Pasterova 2
11000 Belgrade
Serbia
mfolic@yahoo.com

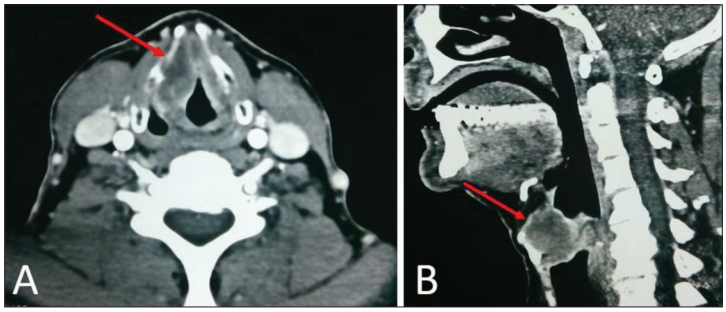

Figure 1. Computed tomography scan of the neck: axial (A) and sagittal view (B); arrows point to laryngeal leiomyosarcoma

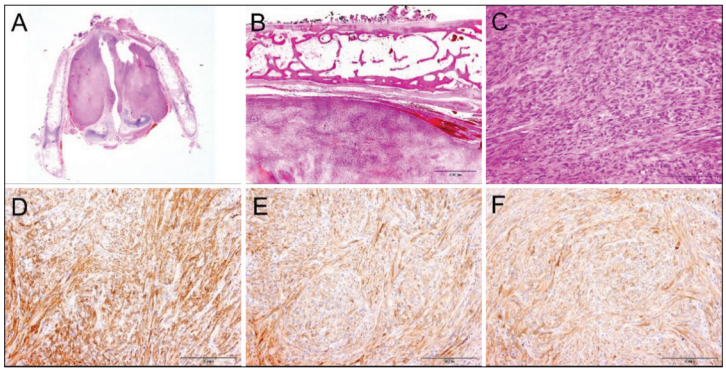

Figure 2. Histopathological finding of laryngeal leiomyosarcoma; hematoxilin-eosin; A – tumor fills paraventricular space (whole organ section); B – but not infiltrates thyroid cartilage; C – tumor is cellular and is composed of fascicles of atypical smooth muscle cells; mitoses are numerous and atypical; Ki67 proliferative index is 40% (not shown); D – tumor is positive for ASMA; E – calponin; F – h-caldesmon

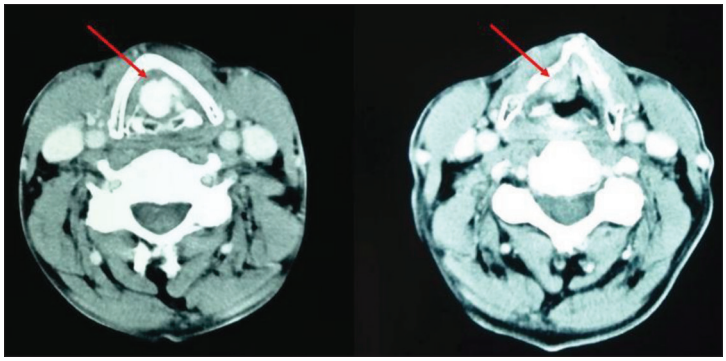

Figure 3. Computed tomography scan of the neck: axial views; arrows point to laryngeal osteosarcoma

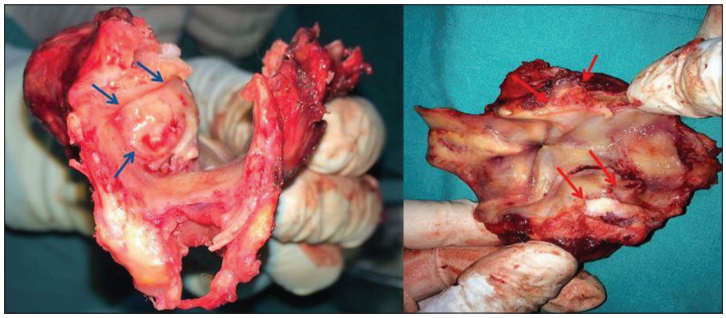

Figure 4. Surgical removal of the larynx with osteosarcoma

laryngeal tumor with bone tissue density (Figure 3). Patient did not have enlarged lymphatic nodes of the neck and total laryngectomy was performed with clear surgical margins (Figure 4). Definitive diagnosis of high-grade laryngeal osteosarcoma (LOS) was made after surgery by a pathologist (Figure 5). The patient was diagnosed with inoperative locoregional relapse of malignant disease three months after surgery and had no distant metastases. Unfortunately, lethal outcome occurred five months after laryngectomy.

CASE OF LARYNGEAL CHONDROSARCOMA

An 87-year-old male visited an ear, nose, throat specialist because of hoarseness that began several months ago. Patient had no history of tobacco or alcohol consumption. Indirect laryngoscopy showed submucosal lesion of the left ventricular and vocal fold with subglottic extension and substantial airway reduction. An expansive lesion of both laminas of thyroid cartilage, as well as cricoid cartilage (size 30 × 37 × 29 mm) with no cervical metastatic lymph nodes was seen on CT scan (Figure 6). Microlaryngoscopy revealed that the lesion is quite hard after submucosal resection and histopathology finding was inconclusive, whether the tumor is chondroma or chondrosarcoma. The patient underwent total laryngectomy and postoperative histopathological analysis confirmed low-grade chondrosarcoma on multiple sites of larynx (Figure 7). Despite his age and tumor extensiveness, the patient had an excellent recovery and mastered the esophageal speech technique with success. Patient was closely controlled and was disease-free during the three-year follow-up.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from all patients.

DISCUSSION

Very low incidence of LLMS has been attributed to the scarcity of smooth muscle tissue. Although it is widely accepted that LLMS originates from vascular smooth muscle in the tunica media of the vessels, some authors reported the aberrant differentiation of mesenchymal tissue as an alternative mechanism in the pathogenesis [5]. Abnormal differentiation after posttraumatic healing process may lead to LLMS formation, although the exact pathway has not been defined yet. Metachronous LLMSs after resection of SCC have been reported and laryngeal

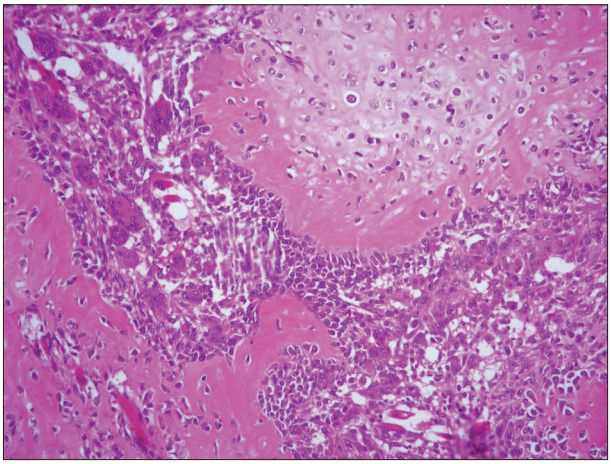

Figure 5. Conventional osteosarcoma, high-grade; Haematoxillin & Eosin, original magnification × 200

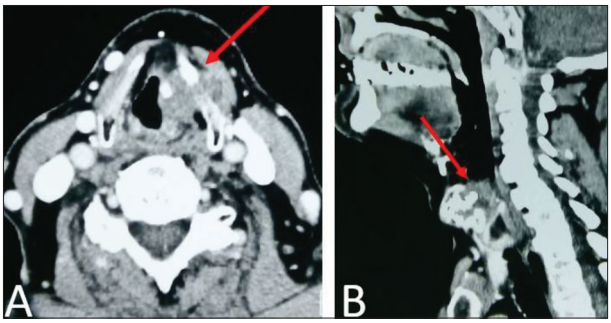

Figure 6. Computed tomography scan of the neck; A – axial; B – sagittal view; arrows point to laryngeal chondrosarcoma

surgery has been identified as a predisposing factor [5]. On the other hand, cases of concurrent LLMS and SCC suggest the involvement of more than one neoplastic process [6].

LOS is considered to originate from immature bone forming cells or after differentiation of chondroblasts and fibroblast into osteoblasts. Skeletal Paget's disease, fibrous dysplasia and previous exposure to the radiation are thought to be a risk factor for LOS development [7]. Further predisposing factors include laryngeal ossification and dedifferentiated chondrosarcomas. Direct correlation between tobacco smoking or alcohol and LOS is no established and the etiology still remains unclear [8].

Laryngeal chondrosarcoma (LCS) arises from cricoid cartilage in 80% of cases [2]. LCSs present with hoarseness in most of the cases. Involvement of the glottis is seen in about 60% of the patients with LLMS and in about 40% of patients with LOS [7], often in combination with supraglottic involvement. It is highly likely that localization of endolaryngeal tumor does not make a significant difference in the clinical outcome. On the other hand, there is a strong correlation between symptoms and tumor sites, so it is expected that any tumor of the glottis might be diagnosed and treated in early stages of the disease, due to its presentation with hoarseness. About one-third of patients with LLMS have dyspnea or stridor at the moment of diagnosis [9]. Other symptoms such as dysphagia, hemoptysis or metastatic lymph nodes are indicators of advanced stage of malignant disease.

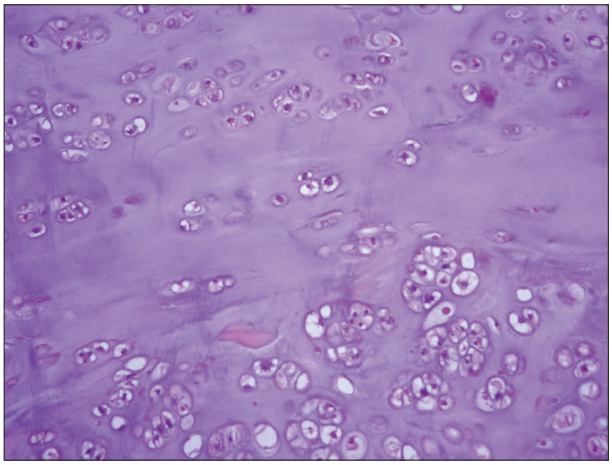

Figure 7. Low-grade malignant mesenchymal proliferation consistent with the diagnosis of chondrosarcoma, Grade 2; Haematoxillin & Eosin, original magnification × 200

Clinical presentation of laryngeal sarcomas should be considered with respect to their biological behavior that differs from SCC. In leiomyosarcomas and osteosarcomas, hematogenous spread of tumor cells is seen far more frequently than lymphatic spread. Furthermore, jugular vein invasion or metastatic deposits in lung and liver may be present without any sign of cervical lymph node involvement. Therefore, it is very important to perform a detailed preoperative evaluation of possible distant metastases and neck dissection is not mandatory in number of cases. On the other hand, LCSs usually present as local disease and distant metastases are quite uncommon, especially in non-aggressive low-grade forms of chondrosarcoma.

Laryngeal sarcomas are macroscopically similar to SCC and definitive diagnosis is made by histopathology. CT and magnetic resonance imaging provide additional information regarding tumor extension and lymph cervical lymph node status. Differential diagnosis of LLMS may be challenging with small biopsies and should include spindle cell tumors, such as rhabdomyosarcoma, melanoma, malignant fibrous histiocytoma or sarcomatous carcinoma [10]. Histologically, leiomyosarcoma is characterized by fascicles of spindle cells with cigar-shaped, blunt-ended nuclei, but light microscopy is insufficient to make an accurate diagnosis [5, 11]. Therefore, immunohistochemistry is mandatory and provides a reliable diagnosis in most cases. Leiomyocytes are positively stained with smooth muscle actin, desmin, and vimentin, whereas stained negatively with cytokeratin and S-100. In most of the LOS cases, multiple biopsies are necessary to achieve a proper diagnosis [8]. Spindle cell sarcoma, metastases from the primary sarcoma, carcinosarcoma and other malignancy with osseous metaplasia should be considered in diagnostic work-up [12]. It is essential to differentiate LCS from chondroblastic osteosarcoma that is characterized by the presence of osteoid material with signs of high-grade malignancy surrounded by hypercellular spindle cells [13]. Also, it is not unusual for chondrosarcoma to be misdiagnosed as laryngeal chondroma.

The primary choice of treatment for laryngeal sarcomas is surgical resection with wide surgical margins. Stage and

localization of malignant disease affect the type and range of surgical procedure. Total laryngectomy showed lower recurrence rate and better prognosis, compared to organ preservation surgery. All of our patients underwent total laryngectomy due to advanced stage of sarcomas, although they had different outcome.

Neck dissection is not recommended, unless there is radiological evidence for regional metastasis. Sarcomas are considered to be radioresistant tumors and no efficacy of postoperative radiation therapy (RT) has been demonstrated in patients with osteosarcoma [7]. There are some evidences regarding the adjuvant use of RT which slightly reduce the risk of local recurrences in patients with LLMS [14]. Conventional RT is proved to be ineffective as treatment of laryngeal chondrosarcoma due to slow-growing nature of the tumor, although it has a role as adjuvant treatment or palliative measure. Furthermore, local control has been achieved by adjuvant RT in 94% of patients with residual tumor after chondrosarcoma resection [15]. The role of chemotherapy as a treatment of laryngeal sarcoma is controversial. Sarcomas are not chemosensitive tumors and chemotherapy is usually reserved for the treatment of distant metastasis and may also provide some benefit where surgery is not an option.

Although the most chondrosarcomas are low grade and are not characterized by aggressive behavior, recurrence rate is reported to be 18–40%. On the other hand, high-grade chondrosarcomas have 70% higher metastatic potential, compared to low-grade chondrosarcomas and are associated with poorer prognosis and 10-year survival rate of 29% [2]. LLMSs showed recurrence rate of 30% with five-year survival rate of 50% [15], whereas mean time to locoregional LOS recurrence and LOS distant metastasis is five months and 12 months, respectively [7]. About half of the patients with laryngeal osteosarcoma die within 20 months after surgery [8].

In conclusion, primary laryngeal sarcomas are rare malignant tumors that differ from SCC by their biological characteristics and behavior. Radical surgical resection remains the mainstay of treatment with uncertain outcome due to their high potential for recurrence or metastatic spread.

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Примарни саркоми ларинкса – приказ три болесника и преглед литературе

Александар Угриновић[1], Александар Тривић[1,2], Владимир Ђорђевић[1,2], Нада Томановић[3], Миљан Фолић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за оториноларингологију и максилофацијалну хирургију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Катедра за оториноларингологију са максилофацијалном хирургијом, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

САЖЕТАК

Увод Примарни саркоми ларинкса су веома ретки и чине око 1% свих ларингеалних малигних тумора. Представљамо три болесника са различитим типовима саркома ларинкса и расправљамо о дијагностичким и терапијским потешкоћама.

Приказ болесника Сва три болесника имала су промуклост и осећај тежег дисања на прегледу. Компјутеризована томографија је код сваког показала велике трансглотисне туморе ларинкса без знакова лимфаденопатије врата, а дефинитивна дијагноза саркома постављена је од стране патолога. Сваки болесник је подвргнут тоталној ларингектомији са слободним линијама ресекције. Болесник са лејомиосаркомом ларинкса развио је велики локорегионални релапс малигне болести и плућне метастазе четири месеца после операције, а болеснику са остеосаркомом ларинкса дијагностикован је иноперабилни локорегионални релапс малигне болести три месеца после операције. Оба болесника су умрла у року од шест месеци након операције. С друге стране, болесник са хондросаркомом ларинкса био је без болести током трогодишњег праћења.

Закључак Примарни саркоми ларинкса имају ниску учесталост и разликују се од сквамоцелуларног карцинома по биолошким карактеристикама и понашању. Радикална хируршка ресекција остаје главни терапијски избор са неизвесним исходом због високог потенцијала за настанак рецидива или метастатског ширења.

Кључне речи: сарком; лејомиосарком; стеосарком; хондросарком; ларингеална неоплазма; ларингектомија

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Vitamin B1, eye and brain

Marija M. Božić[1,2], Marija Milenković[1,3], Dragan M. Pavlović[4], Miroslav Stamenković[4,5], Aleksandra M. Pavlović[1,6]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Center of Serbia, University Eye Hospital, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Emergency Center, Department for Anesthesiology, Belgrade, Serbia;
[4]University of Belgrade, Faculty for Special Education and Rehabilitation, Belgrade, Serbia;
[5]Zvezdara University Clinical Centre, Belgrade, Serbia;
[6]University Clinical Center of Serbia, Neurology Clinic, Belgrade, Serbia

SUMMARY
Vitamin B1 (aneurin, thiamine) is a water-soluble vitamin necessary for the normal function of the nervous system, visual system and heart and is part of important enzymes in the body. Thiamine enables the normal use of glucose, other carbohydrates and proteins, and enables the supply of energy to the organism. The main sources of thiamine are exogenous and small amounts are synthesized by microorganisms of the human intestinal microbiome.
Vitamin B1 cannot accumulate in the body, so signs of deficiency are quickly manifested. Hypovitaminosis B1 is seen in chronic ethyl abuse, persistent vomiting (as in some pregnant women) or after bariatric surgical procedures, but in a mild form it is present in the general population.
Normal daily needs for vitamin B1 depend on calorie intake, and 0.4 mg should be ingested for every 1000 kcal.
Keywords: vitamin B1; eye, brain

INTRODUCTION

Although importance of vitamins for visual function is well known, the importance of all of them is not yet elucidated [1]. Vitamin B1 (aneurin, thiamine) is a water-soluble vitamin that is crucial for glucose metabolism and is necessary for normal growth and development of the organism. Thiamine is essential for functioning of both central and peripheral nervous systems, visual, digestive and cardiovascular systems [2].

The main sources of thiamine are exogenous, with food, and small amounts are synthesized by microorganisms of the human intestinal microbiome [3]. Most thiamine is found naturally in pork and other meats, germ grains, liver, eggs, fish, beans, peas, nuts and whole grains. The recommended daily intake is 0.4 mg per 1000 kcal. Significant amounts of vitamin B1 are lost during heat treatment of food. The polyphenols in coffee and tea can inactivate thiamine. The recommended daily intake of thiamine is 2 mg [2].

Vitamin B1 cannot accumulate in the body, so signs of deficiency are quickly manifested [2]. Thiamine stores in the body are only about 30 mg, with a half-life of 10–18 days [4]. Hypovitaminosis B1 is seen in chronic ethyl abuse, persistent vomiting (as in some pregnant women) or after bariatric surgical procedures, but in a mild form it is present in the general population [5].

PHYSIOLOGY

Vitamin B1 is necessary for normal function of the nervous system, visual system and heart, and is part of important enzymes in the body. Thiamine enables the normal use of glucose, other carbohydrates and proteins, and enables the supply of energy to the organism. Thiamine-dependent enzymes use thiamine diphosphate (ThDP) as a coenzyme. These enzymes are also called ThDP-dependent enzymes. Other thiamine derivatives are thiamine triphosphate and thiamine adenylate, which participate in homeostasis that is the non-enzymatic activity of vitamin B1 [6].

DEFICIENCY

Historically, hypovitaminosis B1 – beriberi, was first described in Japan, several centuries ago, and in the 19th century, Wernicke's encephalopathy and Korsakoff's syndrome [3]. Even today, B1 hypovitaminosis is more common than previously thought, primarily due to the discrepancy between high intake of pure calories and low intake of vitamins, with the situation being exacerbated by the fact that this vitamin deficiency is a major imitator [7]. The modern way of eating "fast" food favors the development of the withdrawal period of vitamin B1. The aggravating factor is the lack of pathognomonic signs and reliable laboratory diagnostics. A study conducted by Williams in

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Correspondence to:
Marija M. BOŽIĆ
Pasterova 2
Belgrade
Serbia
ammilovic@gmail.com

the United States in 1943 showed a significant prevalence of vitamin B1 deficiency in the general population [8].

The most commonly affected systems in thiamine deficiency are the heart, blood vessels, nervous system, eyes, and gastrointestinal system [9]. Periventricular gray matter neurons are particularly sensitive to thiamine deficiency [10]. Damage to the nuclei of the vestibular and abducens nerves may precede B1 encephalopathy with mild ophthalmoparesis and bilateral vestibular damage. Aneurin deficiency leads to pseudohypoxia at the cellular level, and later to dysautonomy in various tissues [7]. In deficiency states, lactates, pyruvate and other substances increase. Thiamine deficiency disrupts the function of nitric oxide which is an important transmitter, especially in the vascular system. Vitamin B1 deficiency has been found to correlate with degeneration of ganglion cells of the brain and spinal cord and reduced retinal ganglion cell layer thickness in animal models [11].

Beriberi

Vitamin B1 deficiency causes beriberi with: weight loss, emotional disorders, changes in perception, weakness of the extremities, irregular heartbeat and tissue edema. Heart failure can be fatal. No sign of beriberi is pathognomonic, and the clinical picture is very variable [7]. There is a division into dry beriberi (neurological) where polyneuropathy predominates and wet beriberi (cardiological) where cardiomyopathy with peripheral edema predominates, although they are often associated [9]. Disorders of the gastrointestinal system are also present.

Beriberi was first described in Japan in people who used glazed rice. Thus, food contained high levels of calories with a lack of other essential nutrients called high-calorie malnutrition [12]. Today, high-calorie malnutrition is not uncommon in the West in obese people, where thiamine deficiency is present in as many as 15–29% of people with mild and nonspecific symptoms [13]. Beriberi can be divided into alcohol-induced and non-alcoholic. At risk are people who use diuretics, e.g., furosemide that enhance vitamin B1 secretion [4].

As a rule, patients with beriberi are pale. Slightly elevated body temperature is due to dysautonomia. At the beginning of the disease, palpitations can occur in exertion or stress, while later they might also occur at rest [7]. Edema may only be mild pretibial with sensitivity to palpation. The heart is enlarged, especially the right side. Diastolic pressure is below 60 mm/Hg, and sometimes even drops to zero, especially in children.

Oxygen saturation becomes low in arterial and high in venous blood, which indicates the role of thiamine in oxygen transport. In the initial stages, the vagal tone is increased, and in the advanced stages, the sympathetic tone. Thus, bradycardia can sometimes be found, and sometimes tachycardia. Changes in the electrocardiogram are seen only in the later stages.

The neurological findings are dominated by signs of damage to peripheral nerves, autonomic, sensory and motor neuropathy [9]. Initially the loss of superficial sensibility for touch can be found due to damage to long fibers ("socks" and "gloves" type) and the vibrational sensibility also suffer. When the process spreads to shorter fibers, the abdomen is also affected, with a vague border of loss. Paresthesia also occurs. Later, the fibers for pain are also affected. Loss of sensibility is in most cases symmetrical, but the dominant extremities are usually affected first.

Nystagmus and decreased visual acuity may be observed in the eyes, followed by narrowing of the visual field. Eventually, optic neuritis may develop with papillary edema and then temporal pallor, similar to multiple sclerosis [3, 14]. Blurred vision and blindness are possible with severe neuropathy.

Patients experience stomach pain and constipation, and in more severe forms anorexia, thirst, nausea and vomiting [15]. There is a disorder in the secretion of the saliva, gastric, and intestinal juices, usually a decrease, due to dysautonomia. Lymphocytosis, neutropenia and eosinophilia can be seen in the blood count. Erythrocyte sedimentation rate is also often elevated. In advanced cases, normoblasts are seen in the peripheral blood.

Wernicke/Korsakoff syndrome

Wernicke's encephalopathy and Korsakoff's dementia/psychosis are often interrelated phenomena caused by vitamin B1 deficiency. Both disorders require urgent treatment, but the diagnosis is often made late or not at all. Autopsy shows pathological findings characteristic of these diseases significantly more common than is the prevalence in both the general population and the ethyl abuse individuals [16]. Korsakoff's psychosis is a severe acute dementia with the impossibility of remembering new information, that is, anterograde amnesia and confabulations and is difficult to treat [9].

Wernicke's encephalopathy manifests itself as global confusion, oculomotor disorder (nystagmus, ophthalmoplegia) and gait ataxia, which is a classic triad that is seen in only 16–20% of cases, so the diagnosis is often wrong [16]. It is especially difficult to diagnose Wernicke's encephalopathy during a drunken state, other causes of confusion, the use of benzodiazepines, sepsis, hypoxia, hepatic encephalopathy, delirium tremens and head injuries. Untreated Wernicke's encephalopathy is fatal in about 20% of cases [17].

Wernicke's encephalopathy and/or Korsakoff's dementia most often occur in chronic alcoholics, followed by a decreasing incidence in cancer, gastrointestinal surgery, Hyperemesis gravidarum, starvation, fasting, gastrointestinal diseases, AIDS, resorption disorders, dialysis and kidney disease, parenteral nutrition, vomiting, psychiatric diseases with eating disorders and schizophrenia, infections, intoxication, thyroid disorders, iatrogenic, poor nutrition, hypoxic encephalopathy, diarrhea, magnesium deficiency, some congenital conditions and other [16].

Marginal thiamine deficiency

Mild forms of thiamine deficiency are common because depos are scarce (liver, muscle) and can occur as early as 2–3 weeks after thiamine-deficient nutrition [9]. Alcohol,

tea and coffee lower thiamine levels as well as higher amounts of carbohydrates. Also at risk are people with increased thiamine needs such as pregnant and lactating women, people exposed to heavy physical exertion, people with cancer, liver, infections and hyperthyroidism, patients undergoing surgical procedures, as well as thiamine resorption disorders (excess alcohol intake, gastrointestinal diseases, vomiting, diarrhea).

Thiamine deficiency can manifest as anorexia, malaise, burning in the extremities distally, irritability and depression, while later, after 2–3 months, insomnia, cough, emotional lability, panic attacks, pain in the joints, muscles or extremities may occur. It also increased need for sugar, gastro-esophageal reflux, abdominal pain with constipation and diarrhea, daily headaches or migraines, edema of the nasal mucosa, dyspnea, polyneuropathy with numbness, paresthesia, cold extremities, palpitations, also chest pain, intolerance to ambient temperature as well as recurrent nausea and vomiting [9, 7].

Chronic vitamin B1 deficiency significantly contributes to the development of neurodegenerative diseases [2]. Thiamine is associated with Alzheimer's disease, Parkinson's disease, Huntington's disease, and Wernicke-Korsakoff syndrome. Thiamine administration not only has a neuroprotective effect but also has a beneficial effect even in advanced neurodegenerative diseases.

Thiamine deficiency in children should be suspected in a whole range of non-specific symptoms such as: emotions, behavior and attention disorders, learning disabilities, redness of the cheeks, pale eyes, blood pressure disorders, muscle reflex disorders, dermographism and others [7].

Benfotiamine

Benfotiamine is a synthetic vitamin B1 that is liposoluble and passes many times better into the brain and peripheral nerves, which makes it suitable in the treatment of nervous diseases [18]. Comparative studies have shown that lipophilic thiamine derivatives are significantly better resorbed than hydrophilic thiamine [19]. Benfotiamine is a liposoluble precursor of thiamine that can be converted to thiamine in tissues and then metabolized to thiamine monophosphate and thiamine diphosphate [20].

The effects of benfotiamine are mild inhibition of cholinesterase, reduction of amyloid plaque production and hyperphosphorylated tau [21, 22]. It also accelerates the recovery of peripheral nerves after various injuries. In an animal model, administration of benfotiamine improved spatial memory in a dose-dependent manner and reduced in Alzheimer's disease model both amyloid beta plaques and hyperphosphorylated tau levels, with other forms of thiamine not being effective. Long-term use of benfotiamine in a small study in patients with Alzheimer's disease improved cognitive status [23].

Benfotiamine has been used successfully in diabetic polyneuropathy [24]. The greatest effect was achieved after 3–6 weeks of administration with large doses of benfotiamine of 320 mg/day, but smaller doses were also effective (150 mg/day). The feeling of pain is reduced and the vibrational sensitivity is improved. Usually, 150 mg twice a day or 300 mg twice a day of benfotiamine is given with food. In some cases of Korsakoff's psychosis, long-term administration of benfotiamine is required with gradual reduction of doses to maintenance doses with excellent results. Benfotiamine can be given up to 600 mg daily.

Sulbutiamine

Another synthetic derivate of vitamin B1, with beneficial effects in treatment of Alzheimer's disease. Sulbutiamine enhances cholinergic and glutamanergic transmission, mainly by hippocampus and prefrontal cortex. Sulbutiamine has proven neuroprotective effect on retinal ganglion cells [25]. This is a highly lipid soluble synthetic analogue of vitamin B1, clinically used for asthenia treatment. When tested on retinal ganglion cells in vitro, it showed effects of preventing trophic factor induced apoptotic cell death. Sulbutiamine is lipophilic and easily crosses the brain blood barrier. Numerous studies showed that this agent stimulates reticular activating system, potentiates cholinergic activity in hippocampus and glutamatergic activity in the prefrontal cortex [26, 27].

Diagnosis of vitamin B1 deficiency

The diagnosis of vitamin B1 deficiency requires, above all, a high degree of suspicion of these disorders in all increased risk conditions because the clinical picture is highly variable [28]. A detailed anamnesis regarding the consumption of food, alcohol, vomiting, digestion, etc., is also necessary, as well as a careful clinical examination. Vitamin B1 testing is based on measuring concentrations: thiamine pyrophosphate or transketolase (thiamine-dependent enzyme) activity in erythrocytes [5].

Well-documented cases of Wernicke's encephalopathy with normal or even elevated thiamine levels have also been described [28]. This is probably due to the discrepancy of levels in serum and tissues, as is the case with vitamin B12 and magnesium [7, 9, 29]. Normal serum thiamine values are 70–180 nmol/L, and deficits indicate values less than 70 nmol/L.

THERAPY

Normal daily needs for vitamin B1 depend on calorie intake: 0.4 mg should be ingested for every 1000 kcal [9]. This would mean e.g., that an adult man who ingests 3200 kcal per day should take 1.3 mg of thiamine per day, and a woman who ingests 2300 kcal to take 0.9 mg of thiamine. Slightly different is the recommendation of the National Research Council from the United States, which states the required intake of 0.5 mg per 1000 kcal, with the proviso that the daily intake should not be less than 1.0 mg regardless of calorie intake.

National Research Council states that due to the additional caloric needs of the fetus, pregnant women should take an additional 0.4 mg per day of thiamine at the

appropriate daily intake, and during lactation, the infant needs another 0.5 mg per day for their own needs [30, 31]. Infants should take 0.17 mg of thiamine daily. The recommendation of the World Health Organization (WHO) is 0.3 mg/L or 0.4 mg/1000 kcal. Children and adolescents have the same needs as adults, i.e., 0.4 mg / 1000 kcal and 0.5 mg/1000 kcal [31].

THERAPEUTIC APPLICATION

Thiamine has been used in patients with: anxiety disorders, chronic fatigue, sleep disorders, anorexia, nausea, indigestion, chest and abdominal pain, depression, aggression, headaches, etc. Some studies have shown a beneficial effect of vitamin B1 in people with neurodegenerative diseases [6]. The benefit of thiamine therapy in Wernicke-Korsakoff syndrome, beriberi and other deficiencies is unequivocal. Prompt thiamine replacement is necessary to prevent irreversible changes [16]. Due to urgency, vitamin B1 is usually applied empirically, especially since the level of B1 in the blood is not a reliable measure of deficiency. Benfotiamine is also used.

There are no generally accepted guidelines for the use of thiamine. There are schemes with the administration of thiamine for prophylactic purposes in persons at risk with 100 mg intramuscularly three times a day for 3–5 days or 250 mg intramuscularly for 3–5 days, as well as many other schemes [16]. In the case of diagnosed Wernicke and/or Korsakoff syndrome, thiamine is administered intravenously in doses of 100–500 mg for at least five days, and then in smaller doses, e.g., 250 mg intramuscularly until improvement occurs. Prolonged oral administration is usually required to achieve better effects. Giving doses of ≥ 500 mg intravenously daily is safe [31]. According to recommendations, in mild deficits, 100 mg should be given orally daily.

In children with vitamin B1 deficiency and heart failure, convulsions or coma, 25–50 mg of thiamine is given very slowly intravenously, then daily 10 mg intramuscularly for one week and then 3–5 mg daily orally for at least six weeks [9].

SAFETY

Excess thiamine is excreted by the kidneys [9]. Isolated cases of adverse reactions have been reported with intravenous administration in doses of 5–100 mg, and very rarely an allergic reaction may occur with extremely high oral doses of 5–10 g [32]. Also, it has been proven that long term use of thiamine supplements (along with other B group vitamins and vitamin A) is associated with reduced prevalence of nuclear and cortical cataract [33, 34]. In this study a supplement user was defined as a subject who consumed vitamin supplements for at least four days per week, with variable dosage 0.8–1 mg/day.

CONCLUSION

Thiamine, or Vitamin B1, is an essential nutrient with many health benefits, especially protecting the brain and heart [33, 34, 35]. Time will tell whether vitamin supplementation, especially thiamine, has an impact on winning the covid pandemic [36]. This is an opportunity for medical workers and ordinary people, to be reminded of its importance, natural sources and possible supplementation.

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Витамин *B*1, око и мозак

Марија М. Божић[1,2], Марија Миленковић[1,3], Драган М. Павловић[4], Мирослав Стаменковић[4,5], Александра М. Павловић[1,6]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетски клинички центар Србије, Клиника за очне болести, Београд, Србија;
[3]Универзитетски клинички центар Србије, Ургентни центар, Центар за анестезију, Београд, Србија;
[4]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[5]Клиничко-болнички центар Звездара, Београд, Србија;
[6]Универзитетски клинички центар Србије, Клиника за неурологију, Београд, Србија

САЖЕТАК

Витамин *B*1 (анеурин, тиамин) растворљив је у води, неопходан је за нормално функционисање нервног система, органа вида и срца и део је важних ензима у телу. Тиамин омогућава нормалну употребу глукозе, других угљених хидрата и протеина и снабдевање организма енергијом.

Главни извори тиамина су егзогени и мале количине синтетишу микроорганизми људског цревног микробиома.

Витамин *B*1 се не може накупљати у телу, па се знакови недостатка брзо манифестују. Хиповитаминоза *B*1 се опажа код хроничне злоупотребе алкохола, упорног повраћања (као код неких трудница) или после баријатријских хируршких процедура, али у благом облику је присутна и у општој популацији.

Нормалне дневне потребе за витамином *B*1 зависе од уноса калорија, па на сваких 1000 *kcal* треба унетити 0,4 *mg* овог витамина.

Кључне речи: витамин *B*1; око; мозак

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IN MEMORIAM

Professor Miodrag Colić, MD, PhD. 1957–2021

One of the most prominent plastic surgeons both in Serbia and internationally, Miodrag Colić was born on May 14, 1957, in Pirot, Serbia. He finished primary school and high school in Belgrade as a straight-A student, at the time having won four October Awards and one award presented by the journal *Politika* for literature.

Miodrag Colić enrolled at the University of Belgrade, Faculty of Medicine in 1976, and graduated in 1982, with an average grade of 9.85. During his studies, he received one Faculty of Medicine award and two University awards for his academic success, as well as two awards from the *Medicinski podmladak* student magazine for the professional papers he published in it. In 1985, after the opening of the Clinic for Burns, Plastic, and Reconstructive Surgery in Belgrade, Professor Colić had started his permanent employment. He worked there until 2012. From 2001 until 2009, he was the Head of the Clinic.

Miodrag Colić completed his plastic and reconstructive surgery program in April of 1987 at the Faculty of Medicine in Belgrade, and passed his specialist exam with the highest honors. In June of 1987, he graduated with a Master's degree from the Faculty of Medicine in Belgrade with the paper titled *Diagnostic and Therapeutic Aspects of Disorders in Breast Development*. In October of 1994, he became Ph.D. with paper *The Role of Hyperbaric Oxygenation in the Treatment of Electrical Injuries*. He was appointed an Assistant at the Department of Surgery at the Faculty of Medicine in Belgrade in November 1991. In 1998 he was elected an Assistant Professor, then, was elected a Professor.

Miodrag Colić sought his professional training in Plastic and reconstructive surgery with Prof. J. Aviles Velastegui at the Plastic Surgery Department, Gregorio Maranon Hospital, Madrid and with Prof. B. Vilar-Sancho, Sanatorio Nuestra Señora de la Paloma, as a Spanish Government fellowship holder. With Prof. F. Ortiz-Monasterio at the Cranio-Maxillofacial Surgery Department in Manuel Gea González Hospital, as well as Ángeles Hospital, Aesthetic & Plastic Surgery Department, Tijuana, Mexico, as a Mexican Government fellowship holder. He was a friend and student of the famous plastic surgeon Dr Ivo Pitangy in Centro de Estudios Ivo Pitanguy, Rio de Janeiro, as well as Breast Surgery Centre, Sao Paulo, Brazil.

Figure 1. Professor Miodrag Colić, MD, PhD. 1957–2021

Miodrag Colić was appointed a member of the International Society of Aesthetic Plastic Surgery Board of Directors in the capacity of the Chair of the National Secretaries 2004–2008, Secretary General 2008–2012 and Vice-Chair 2012–2013. In 2011, he became the European Representative with the International Confederation for Plastic Reconstructive and Aesthetic Surgery as well as a member of the Committee on Cooperation with International Organizations. Professor Colić is one of the founders of the Balkan Society for Plastic Surgery. Since 2009, when the Serbian Breast Reconstruction Society was established, he has been its President.

Professor Miodrag Colić was a member of the International College of Surgeons,

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Correspondence to:
Milan STOJIČIĆ
Clinic for Burns, Plastic and Reconstructive Surgery
University Clinical Centre of Serbia, Belgrade, Serbia
Zvečanska 9
11000 Beograd Srbija
milan.stojicic@med.bg.ac.rs

International Confederation for Plastic, Reconstructive and Aesthetic Surgery, International Society of Aesthetic Plastic Surgery, American Society for Aesthetic Plastic Surgery, New York Academy of Sciences, European Academy of Cosmetic Surgery, Serbian Medical Association and many others. He was an honorary professor at the Albert Schweitzer International University and Professor and Provost at the Lipoplasty University.

He was the President of the international aid organization Lions Club International for Yugoslavia in 2001–2002 and Serbia and Montenegro in 2003–2004.

Miodrag Colić has published over 200 professional papers and four monographs. As he pursued surgical career, he was also very much engaged in writing poetry and exploring new worlds. He is the author of the book of poems *The Trail of Eternity* as well as the two-volume monograph *My journey around the world.*

Together with his brother, Milan Colić MD., Professor Miodrag Colić was a co-owner of Hospital for Plastic, Reconstructive and Aesthetic Surgery *Colić.* Since 2010, he has been the Honorary Consul of the Republic of Peru. Professor Colić spoke many languages. He was fluent in English and Spanish.

Miodrag Colić was an artist, a poet at heart and a maestro with the scalpel. He was a great man, a loving friend, and a masterful doctor full of passion for his craft. His indomitable spirit led him constantly forward. As a world traveler, he visited all of the countries around the world.

After battling a long illness, he died in Colombo, Sri Lanka on September 24, 2021. His work continues to live on through countless patients whose lives he had improved, saved even, as well as his sons Filip and Konstantin. Konstantin Colić MD, is following in his father's footsteps as a future plastic surgeon.

We were incredibly fortunate and eternally grateful to have had him in our lives. May his memory be eternal.

Milan T. Stojičić,
Clinic for Burns, Plastic and Reconstructive Surgery
University Clinical Centre of Serbia, Belgrade, Serbia
University of Belgrade, Faculty of Medicine, Belgrade, Serbia
Milan D. Jovanović,
Clinic for Burns, Plastic and Reconstructive Surgery
University Clinical Centre of Serbia, Belgrade, Serbia
University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

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The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*http://www.nlm.nih.gov/mesh*) are to be used for selection of the keywords.

TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

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Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
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