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SINKOPA KOD DECE

SYNCOPE IN CHILDREN

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Sažetak: Sinkopa se definiše kao nagli, prolazni i kratkotrajni gubitak svesti. **Cilj:** Utvrditi učestalost sinkopa kod dece školskog uzrasta, njihovu starosnu i polnu strukturu kao i okolnosti pod kojima je došlo do sinkope. **Materijal i metode:** Studija preseka u kojoj su praćena deca školskog uzrasta sa teritorije opštine Inđija, u periodu jun-decembar 2017. Istraživanje je obuhvatilo samo decu kod koje je sinkopa registrovana u sklopu prve posete pedijatru. **Rezultati:** Registrovana su ukupno 22 prva pregleda zbog sinkope, što čini 0,83% od ukupnog broja prvih pregleda (2640) u ispitivanom periodu. Rekurentna sinkopa se javila u tri slučaja. U polnoj strukturi su dominirale devojčice - 14 (63,6%) u odnosu na 8 (36,4%) dečaka, ali bez statistički značajne razlike po polu. Sinkopa je najčešće registrovana u uzrastu od 14 godina, njih četvoro (18,4%) pacijenata, a nije registrovana u uzrastima od 11 i 19 godina, bez statističke razlike u odnosu na starosnu strukturu. Srednje godište bilo je 13,5 godina. Okolnosti koje su predhodile sinkopi: nakon naglog ustajanja kod 4 pacijenta (18,2%) a nakon fizičke aktivnosti kod 5 (22,7%). Od ukupnog broja registrovanih ispitanika sa sinkopom njih 12 (54,5%) upućeno je na dopunsko ispitivanje. Kod 15 ispitanika (68,1%) se radilo o nekoj vrsti refleksne sinkope, ali se i preostali slučajevi mogu objasniti relativno bezazlenim uzrocima. **Zaključak:** U ispitivanom periodu 22 pacijenta (0,83%) od ukupnog broja prvih pregleda javilo se pedijatru zbog sinkope. U polnoj strukturi su dominirale devojčice, samo kod tri pacijenta su bile rekurentne sinkope a srednje godište ispitanika bilo je 13,5 godina. Okolnosti koje su prethodile sinkopi upućuju na zaključak da se u najvećem broju radilo o refleksnoj sinkopi. Od ukupnog broja 12 (54,5%) upućeno je na dopunsko ispitivanje.
Ključne reči: sinkopa, sinkopa/okolnosti, dopunsko ispitivanje, pedijatar

Summary: Syncope is defined as a sudden, transient and brief loss of consciousness. **The aim** is to determine the incidence of syncope in children of school age, age and gender structure, as well as the circumstances under which syncope occurred. **Material and methods**. This is a cross-sectional study in which school-age children from the municipality of Indjija were monitored in the period between June and December 2017. The survey included only children with the syncope which was registered during the first visit to the pediatrician. **Results:** A total of 22 first screenings due to syncope were registered, which makes 0.83% of the total number (2640) of initial examinations in the given period. The recurrent syncope occurred in three cases. As for gendre structure, most were female, 14 girls (63.6%) in comparison to 8 boys (36.4%), but without a statistically significant gender structure. Syncope was the most common with 14-year-old children – four of them (18.4%), and it was not registred at the age of 11 and 19, without a statistically significant age structure. The average age was 13.5. The circumstances that preceded the syncope: in 4 patients (18.2%) syncope was caused by standing up suddenly, and in 5 patients (22.7%) by physical activity. 12 patients out of total number of patients with syncope, were sent for additional examination. 15 patients (68.1%) had a kind of reflex syncope, and the remaining cases can be explained by relatively harmless causes. **Conclusion.** During the evaluation, 22 patients (0.83%) out of the total number of initial examinations visited his /her pediatrician due to syncope. Most of them were female and the average age was 13.5. Circumstances that preceded syncope suggest that the most common was the reflex syncope. 12 patients (54.5%) were sent for additional examination.
Key words: syncope, syncope/circumstances, additional examination, pediatrician

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UVOD

Sinkopa se definiše kao nagli i prolazni gubitak svesti koji se pripisuje globalnoj cerebralnoj hipoperfuziji. Praćena je gubitkom posturalnog tonusa. Karakteriše se brzim početkom, kratkotrajnošću i spontanim oporavkom. U praksi se za sinkopu često koristi sinonim „kolaps" [1, 2, 3, 4, 5, 6, 7, 8].

Sinkopa nije bolest sama za sebe, već je nespecifični simptom različitih poremećaja. Ova činjenica u značajnoj meri otežava dijagnozu sinkope. Za lekare koji se sa njom susreću u svakodnevnom radu predstavlja diferencijalno dijagnostičku dilemu. Danas se sinkopa često razmatra u grupi tranzitornih kratkotrajnih gubitaka svesti (TLOC) i spada među njihove najčešće razloge. Kod dece se ona najčešće razmatra u grupi stanja koja imitiraju epileptičke napade, ili u grupi paroksizmalnih neepileptičkih poremećaja. U grupu tranzitornih događaja koji klinički liče na epileptičke napade, pored sinkopa se ubrajaju i apneje u spavanju, respiratorne afektivne krize i narkolepsija. Ono što razlikuje sinkopu od drugih oblika TLOC je jedinstvena patofiziologija, a to je prolazna globalna cerebralna hipoperfuzija uzrokovana malom perifernom rezistencijom i/ili malim minutnim volumenom srca (cardiac output) [1, 4, 5, 9, 10, 11, 12].

Sinkopa je tipično kratkog trajanja. Period kompletnog gubitka svesti kod tipične sinkope obično ne traje duže od 20 sekundi. Ukoliko gubitak svesti traje duže, može se javiti tonička ukočenost ili nekoliko simetričnih ili asimetričnih trzajeva ekstremiteta („konvulzivna sinkopa"). Takvo stanje predstavlja poseban dijagnostički problem. Najčešće ova motorna aktivnost nije epileptičke prirode, već se pretpostavlja da nastaje usled oslobađanja centara u moždanom stablu od kortikalne inhibicije [3, 5].

Sinkopa je čest problem, javlja se kod oko 40% opšte populacije najmanje jednom u toku života. Smatra se da će 15-20% dece i adolescenata doživeti sinkopu. Prvi skok incidence je oko 15. godine, češće kod devojčica. Manji skok može se videti kod starije odojčadi i male dece. Ovaj skok obično se objašnjava pojavom respiratornih afektivnih kriza u tom uzrastu. Kumulativna incidenca se povećava sa godinama života. Incidenca sinkope kod dece i mladih koji se jave lekaru iznosi 0.5-3/1000 (0.05-0.3%). Procenjuje se da je broj onih koji se ne jave lekaru znatno veći. Novije studije ukazuju da je oko 20% muškaraca i oko 50% žena prijavilo da je doživelo najmanje jednu epizodu sinkope. Sinkopa predstavlja čest razlog poseta hitnim službama-1-5% i 1-6% prijema u bolnicu. Prvenstveni razlog hospitalizacije je evaluacija kardiološke i cerebralne etiologije. Prema nekim podacima čak 47% otpusti se bez jasne dijagnoze [2, 4, 9, 11, 12, 13, 14, 15, 16]. Najveći broj uzroka sinkope je benigan i samoograničavajući. Iako je većinom benigna u dečjem uzrastu, sinkopa predstavlja alarmantan događaj za decu, roditelje, ali i lekare. Ipak, neki uzroci sinkopa mogu biti udruženi sa značajnim morbiditetom i mortalitetom. Posebnu pažnju treba posvetiti kako bi se bezazleni uzroci sinkopa razlikovali od ozbiljnih neuroloških, kardioloških i metaboličkih poremećaja. U praksi se to najčešće odnosi na razlikovanje sinkope i epilepsije ili ozbiljnih kardioloških poremećaja koji mogu rezultirati iznenadnom srčanom smrti. Razlikovanje sinkope i epilepsije može biti teško, čak i kada su prisutni svedoci napada, pa i medicinsko osoblje [2, 3, 4, 5, 9, 10, 11, 13, 18]. Danas se sve češće primenjuju vodiči i različiti sistemi skorovanja sa ciljem diferencijalne dijagnoze sinkopa i predviđanja ozbiljnih uzroka i posledica sinkopa. Prvi vodiči Evropskog kardiološkog društva (ESC) za sinkopu objavljeni su 2001, a potom revidirani više puta. Najnoviji je izašao 2018. godine. Više skoring sistema razvijeno je za razlikovanje sinkope i epilepsije, od kojih neki imaju senzitivnost i specifičnost 94%. Najveća verovatnoća za epileptički napad je kod osoba kod kojih je registrovan ugriz jezika. Nekoliko studija je pokušalo da predvidi pacijente sa mogućim ozbiljnim ishodom, u kratkom ili nešto dužem praćenju. Najčešće primenjivan je San Francisco Syncope Rule (SFSR), koji ima senzitivnost od 96% i specifičnost od 62%, dok je njegova negativna prediktivna vrednost 99,7% i može biti veoma korisna da smanji broj prijema u bolnicu. Sinkopu možemo klasifikovati na više načina: po etiologiji, mehanizmu, patofiziologiji (tabela 1). Najbolji uvid možemo dobiti uporednim prikazom klasifikacije po etiologiji i mehanizmu (grafikon 1). Klasifikacija na osnovu etiologije ne korelira uvek sa klasifikacijom na osnovu mehanizma. Isti mehanizam sinkope može biti prisutan kod različitih etiologija i obrnuto [1, 2, 3, 5, 9, 11].

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Tabela 1. Klasifikacija sinkope (modifikovano iz ref 5)
Table 1. Classification of syncope (modified from ref 5)

Refleksna (neuralnog porekla)
Vazovagalna: *posredovana emocionalnim stresom: strah, bol, fobija od krvi *posredovana ortostatskim stresom Situaciona: *kašalj, kijanje *gastrointestinalna stimulacija: gutanje, defekacija, visceralni bol *mikcija *posle vežbanja *postprandijalna *drugo: sviranje duvačkih instrumenata, smeh, dizanje tegova Sinkopa karotidnog sinusa Atipične forme (bez vidljivih trigera i/ili sa atipičnom prezentacijom)
Sinkopa uzrokovana ortostatskom hipotenzijom
Primarni autonomni poremećaji Sekundarni autonomni poremećaji Lekovima uzrokovana ortostatska hipotenzija: alkohol, vazodilatatori, diuretici, antidepresivi Gubitak volumena: hemoragija, dijareja, povraćanje
Kardijalna (kardiovaskularna) sinkopa
Aritmija kao primarni uzrok *bradikardija: disfunkcija sinusnog čvora, bolest sprovodnog sistema *tahikardija: supraventrikularna, ventrikularna Srčana: valvularna bolest, akutna ishemija miokarda, hipertrofična kardiomiopatija, urođene anomalije koronarnih arterija Drugo: plućna embolija, plućna hipertenzija

Vazovagalna (refleksna) sinkopa je najčešća kod dece, pogotovo školskog uzrasta. Javlja se usled naglo nastale nemogućnosti autonomnog nervnog sistema da održi arterijski krvni pritisak i ponekad frekvencu srčanog rada na nivou potrebnom da se očuva adekvatna moždana perfuzija i stanje svesti. Karakterišu je precipitirajući faktori (bol, trauma, intenzivna fizička aktivnost, dugotrajno stajanje, emocionalni stres) i neposredno pre nastanka sinkope premonitorni simptomi (malaksalost, nesvestica, preznojavanje, zamućenje vida, muka). Nastaje uvek u uspravnom položaju nakon nekog od precipitirajućih faktora. Dete obično prvo ima omaglicu, ili neki drugi simptom, potom mlitavo pada, nepomično je bledo i oznojeno. Gubitak svesti je obično kratkotrajan [1, 2, 3, 5, 16].

Sve trenutno aktuelne domaće i strane preporuke i vodiči, navode kao osnovnu komponentu u inicijalnoj evaluaciji sinkope: sveobuhvatnu medicinsku i porodičnu anamnezu (uključujući i anamnezu samog događaja), fizikalni pregled i EKG pregled. Smatra se da neke anamnestičke informacije mogu biti veoma značajne u evaluaciji sinkopa i čak sugerisati dijagnozu. Detaljan fizikalni pregled veoma često obuhvata, pored klasičnog pregleda, i merenje ortostatskog krvnog pritiska nakon što bolesnik provede neko vreme u ležećem položaju. Merenje se nastavlja u uspravnom položaju. Smanjenje sisitolnog pritiska za 20mmHg ili smanjenje apsolutne vrednosti sistolnog pritiska ispod 90mmHg definišu ortostatsku hipotenziju, bez obzira da li se simptomi javljaju ili ne. Elektrokardiografija se preporučuje kod svih osoba koje su imale sinkopu. Laboratorijsko ispitivanje krvi se koristi kada postoji sumnja na metabolički uzrok sinkope. Dopunska ispitivanja kao što su 24h

holter monitoring testiranje uz pomoć tilt stola, elektroencefalografija, CT mozga, psihijatrijsko ispitivanje se ređe koriste [1, 2, 3, 5, 9, 10, 13, 16].

Terapija sinkope se može podeliti na nemedikamentnu i medikamentnu. Nemedikamentna terapija, pre svega, podrazumeva adekvatan unos soli i vode, izbegavanje situacija koje mogu biti okidač, redovno vežbanje, „ortostatski trening". Medikamentna terapija podrazumeva primenu lekova kao što su alfa agonisti, beta blokeri [3, 9, 16, 17].

Cilj istraživanja je da se utvrdi učestalost sinkopa kod dece školskog uzrasta, uzrastna i polna struktura kao i okolnosti pod kojima je došlo do sinkope.

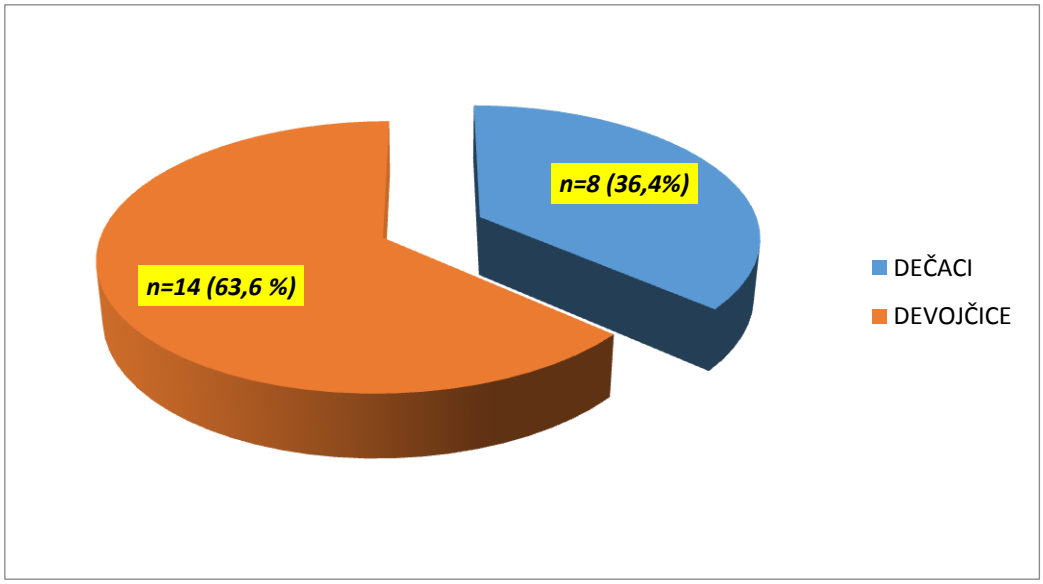
MATERIJAL I METODE

Istraživanje je definisano kao studija preseka u kojoj su praćena deca školskog uzrasta (osnovnih i srednjih škola) sa teritorije opštine Inđija. Praćena su deca uzrasta 6-19 godina koja su posetila školski dispanzer Doma zdravlja „Dr Milorad Mika Pavović" u Inđiji, u periodu jun - decembar 2017. godine. Istraživanje je obuhvatilo samo decu kod koje je registrovana sinkopa u sklopu prve posete pedijatru.

REZULTATI

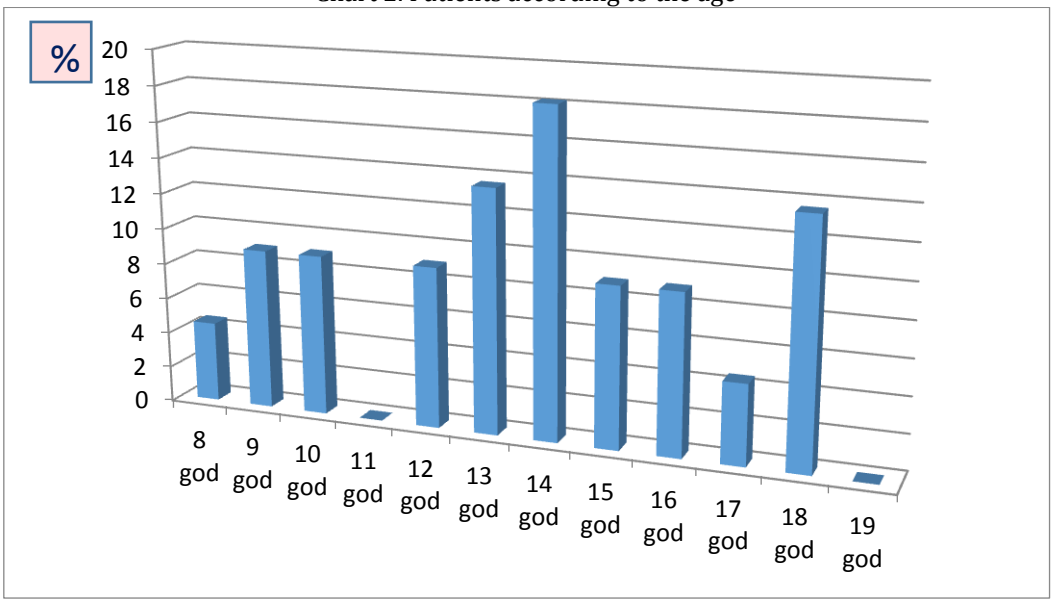
U navedenom periodu registrovana su 22 prva pregleda zbog sinkope, što čini 0,83% od ukupnog broja od 2640 prvih pregleda. Sinkopa je registrovana kod 22 različita pacijenta, 8 dečaka (36,4%), a 14 devojčica (63,6%). Kod 3 pacijenta registrovane su ponavljane epizode sinkope. (Grafikon1).

Grafikon 1. Polna struktura ispitanika
Chart 1. Gender structure of respondents



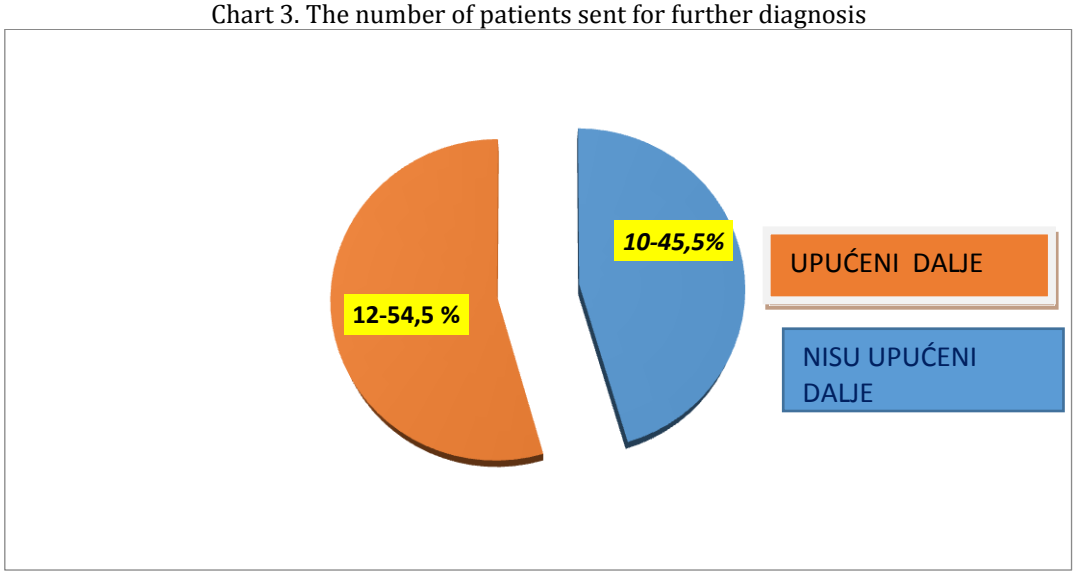
Od ukupnog broja registrovanih pacijenata sa sinkopom jedan (4,5%) je uzrasta 8 godina, dvoje (9%) su uzrasta 9 godina, dvoje (9%) su uzrasta 10 godina; u uzrastu od 11 godina nije bilo registrovanih pacijenata; dvoje (9%) su uzrasta 12 godina; troje (13,8%) su uzrasta 13 godina; četvoro (18,4%) su uzrasta 14 godina; dvoje (9%) su uzrasta 15 godina, dvoje (9%) su uzrasta 16 godina; jedan (4,5%) je uzrasta 17 godina i troje (13,8%) su uzrasta 18 godina. Srednje godište pacijenata sa sinkopom bilo je 13,5 godina (Grafikon2.). Nema statistički značajne razlike u učestalosti prvih pregleda zbog sinkope prema uzrastu. (Hi kvadrat test- $\chi 2$: DF=2, P=0,05; X=2,02, granična vrednost=5,991).

Grafikon 2. Prikaz pacijenata po godištima
Chart 2. Patients according to the age



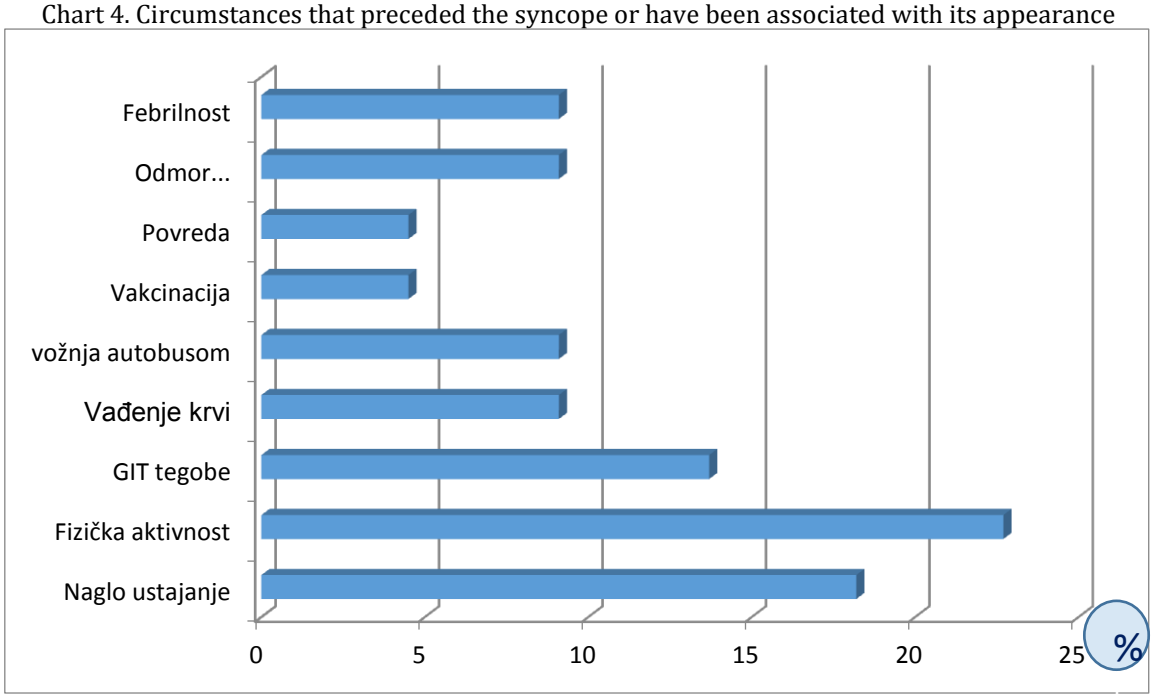
Kod svih ispitanika primarna evaluacija sinkopa obuhvatila je: fizikalni pregled, EKG, TA i osnovne laboratorijske analize. Od ukupnog broja ispitanika njih 10 (45,5%) nije upućeno na dalje ispitivanje, dok je 12 ispitanika (54,5%) upućeno na dopunsko ispitivanje u ustanovu sekundarnog ili tercijarnog nivoa (Grafikon 3). Najveći broj od ukupnog broja upućenih na dopunsko ispitivanje, njih 8 (66,7%) upućeno je kardiologu. Jedan ispitanik je upućen kardiologu i neurologu, jedan psihijatru i dva ispitanika hirurgu.

Grafikon 3. Procenat pacijenata koji su upućeni na dalju dijagnostiku
Chart 3. The number of patients sent for further diagnosis



Do sinkope je došlo nakon naglog ustajanja kod 4 pacijenta (18,2%); nakon fizičke aktivnosti kod 5 (22,7%); nakon gastrointestinalnih tegoba (proliv i povraćanje) kod 3 (13,7%); nakon vađenja krvi kod 2 (9,1%); tokom vožnje u autobusu kod 2 (9,1%); nakon vakcine kod 1 (4,5%); nakon povrede kod 1 (4,5%); na odmoru u školi kod 2(9,1%); u toku febrilnosti kod 2 pacijenta (9,1%) (Grafikon4).

Grafikon 4. Stanja koja su prethodila sinkopi ili su bila povezana sa njenom pojavom
Chart 4. Circumstances that preceded the syncope or have been associated with its appearance



DISKUSIJA

Podaci o učestalosti sinkopa kod dece uglavnom su dobijani retrogradno, kroz upitnike ili različite procene. Takve procene kreću se u dosta širokom rasponu. Od toga da će do 20% dece i adolescenata doživeti epizodi sinkope do 20. godine, do toga da će se kod 40% opšte populacije pojaviti sinkopa najmanje jednom u toku života [2, 7, 9, 11, 15]. Tokom istraživanja pokušali smo da takve podatke dobijemo odmah od zdravstvene službe. Razultate o broju sinkopa kod dece školskog uzrasta prikazali smo u odnosu na broj prvih pregleda radi lečenja u navedenom periodu. Kada se podaci o broju i učestalosti sinkopa kod dece pokušaju prikazati nešto preciznije, u odnosu na procene, dobijaju se manji procenti. To svakako ne smanjuje značaj ovog problema, kao i efekat koji ostavlja. Takođe treba podsetiti da se veliki broj dece sa ovakvim problemom i ne javi zdravstvenoj službi, a da se jedan broj dece javi u službu hitne medicinske pomoći. Većina istraživanja navodi da se radi o relativno čestom problemu sa kojim se susreću lekari u hitnim službama, i da čini 1-5% poseta hitnim službama. Takođe se navodi da predstavljaju 1% poseta uže specijalizovanim pedijatrijskim hitnim službama [6, 12, 13, 14, 15, 16]. Našim istraživanjem dobili smo podatak da se 0,83% dece u posmatrom periodu javilo na prvi pregled radi lečenja zbog sinkope. Nešto manji broj može se objasniti i činjenicom da se jedan broj dece na prvi pregled, zbog sinkope, nije javio pedijatru već službi hitne medicinske pomoći. Takođe se navodi podatak da problem sinkopa kod dece predstavlja razlog za prijem u bolnicu kod 1-6% dece. Takva deca se prvenstveno hospitalizuju radi evaluacije kardiološke i cerebralne etiologije [6, 13, 14]

Srednje godište naših ispitanika sa sinkopom iznosi 13,5 godina, a najveći broj ispitanika-18,4%, imao je 14 godina. Sinkopa se češće javljala kod devojčica (63,6%). Dobijeni podaci odgovaraju većini podataka u literaturi gde se navodi da je sinkopa češća kod osoba ženskog pola sa skokom učestalosti u uzrastu 15-19 godina [4, 15, 16]. Srednje godište naših ispitanika je bilo veće nego u nekim drugim studijama u kojima je srednje godište iznosilo 10 godina i 6 meseci [7].

Većina ispitanika, njih 54,5%, nakon inicijalne evaluacije je upućena na dopunsko ispitivanje. Najveći broj upućenih (66,7%) upućeno je kardiologu. Objašnjenje za nešto veći broj ispitanika koji su upućeni kardiologu može biti u činjenici da je kod najvećeg broja ispitanika 22,7% fizička aktivnost prethodila sinkopi. Grupi situacionih sinkopa pripada i sinkopa posle vežbanja. Ovde treba imati na umu

da, pored brojnih pozitivnih efekata fizičke aktivnosti i iznenadna srčana smrt najčešće nastupa u toku ili neposredno posle fizičke aktivnosti[19]. Treba napomenuti da je troje ispitanika pre sinkope već imalo postavljenu dijagnozu prolapsa mitralne valvule (PVM), a da je ta dijagnoza postavljena kod još dvoje nakon dopunske evaluacije sinkope. Poznata je činjenica da se sinkopa češće javlja kod osoba sa PVM [20]. Kod ispitanika koji je upućen psihijatru postavljena je dijagnoza psihijatrijskog poremećaja. Ispitanici koji su upućeni hirurgu, upućeni su radi saniranja povreda nastalih sinkopom.

Ipak, na osnovu našeg ispitivanja jasno se može zaključiti da se kod najvećeg broja ispitanika, njih 15 (68,1%) radilo o nekoj vrsti refleksne sinkope (nakon naglog ustajanja, nakon fizičke aktivnosti, nakon vađenja krvi, tokom vožnje u autobusu, nakon vakcine, nakon povrede). Preostale okolnosti koje su prethodile sinkopi (u toku febrilnosti, na odmoru u školi, nakon proliva i povraćanja) takođe se mogu objasniti relativno bezazlenim uzrocim sinkopa kao što su emocionalni stres ili gubitak volumena sa posledičnom hipotenzijom.

ZAKLJUČAK

Našim istraživanjem utvrdili smo da se od ukupnog broja prvih pregleda u navedenom periodu, 0,83% javilo zbog sinkope. Devojčice su i u našem ispitivanju činile većinu 63,6%. Srednje godište ispitanika sa sinkopom iznosilo je 13,5 godine. Okolnosti koje su prethodile sinkopi u najvećoj meri upućuju na zaključak da se radi o refleksnoj sinkopi, ali i veliki broj ispitanika upućenih na dopunska ispitivanja, 54,5%, navodi na zaključak da je potrebna dodatna i kontinuirana edukacija zdravstvenih radnika o ovom problemu.

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ZASTUPLJENOST POSTURALNIH POREMEĆAJA KOD DECE MLAĐEG ŠKOLSKOG UZRASTA

THE PRESENCE OF POSTURAL DISORDERS IN CHILDREN OF THE YOUNGER SCHOOL AGE

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Sažetak: Cilj istraživanja je bila procena posturalnog statusa dece mlađeg školskog uzrasta Osnovne škole "Ivo Lola Ribar" iz Novog Sada. Uzorak ispitanika čini 61 učenik prvog razreda, 33 dečaka i 28 devojčica hronološke starosti 8,5 godine. Za procenu posturalnog statusa primenjena je modifikovana vizuelna metoda Napoleona Volanskog. Rezultati istraživanja pokazuju da ispitanici nemaju znatno odstupanje od dobrog držanja tela kada su u pitanju kifo-lordoza i ravna leđa, a dijagnostikovana su kako mala tako i znatna odstupanja od dobrog držanja kod kifotičnog i lordotičnog lošeg držanja tela. U odnosu na pol, dobro držanje ima 84,8 % dečaka, što je manje od devojčica - 92,9 %. Kod posturalnih poremećaja u frontalnoj ravni najzastupljenija je desna grudna skolioza gde je nadjena statistički značajna razlika između polova. Kod deformiteta grudnog koša dominirale su izdubljene grudi (pectus excavatus) - 83,6%. Najmanje zastupljen poremećaj grudnog koša u ispitivanom uzorku su ispupčene grudi (pectus carinatus). Razlike u polu nisu statistički značajne. Najzastupljeniji posturalni poremećaj nogu u ukupnom uzorku ispitanika su „ X“ noge (Genu valgum), bez statitički značajne razlike u polnoj strukturi. Najmanje zastupljen posturalni poremećaj nogu bio je “O” noge (Genu varum)
Ključne reči: Posturalni poremećaji, skolioza, kifoza, lordoza, genu valgum, genu varum

Summary: The aim of the research was to assess the postural status of the younger school age children of the Elementary School "Ivo Lola Ribar" from Novi Sad. The sample consists of 61 first grade pupils - 33 boys and 28 girls whose chronological age is 8.52. For the assessment of postural status, the modified visual method of Napoleon Volanski was applied. The results of the study show that subjects do not have a significant deviation from the good posture of the body when it comes to kypho-lordosis and straight back, and a little and significant deviation from good posture in the cyphotic and lordotic poor posture. Regarding gender, 84.8% of boys have good posture, which is less than girls - 92.9%. In postural disorders in the frontal plane, the most common is the right chest scoliosis with statistically significant gender difference. In case of thoracic deformities, chest deformity occurs in 83.6% of the total number of children. The lowest incidence of chest disorder in the examined sample was pectus carinatus. Gender differences are not statistically significant. The most common postural leg disorder in the overall sample of subjects is "X" legs. Gender differences are not statistically significant, while the most uncommon disorder is the "O" legs.
Key words: postural disorders, scoliosis, kyphosis, lordosis, genu valgum, genu varum,

UVOD

Posturalni status ima veoma veliki značaj u funkcionisanju ljudskog organizma. Obrazac dobrog držanja tela, ukoliko se stvori u ranom detinjstvu, ne samo da doprinosi pravilnom rastu i razvoju dece, već se kasnije pozitivno odražava na njihovo zdravlje i kvalitet življenja. Formiranje pravilne posture, pored raznih drugih poznatih činilaca, zavisi uveliko od angažovanja učitelja, profesora i roditelja, ali i nivoa fizičke aktivnosti [1]. Zbog lošeg držanja tela kod dece se u kasnijem životnom dobu mogu javiti zdravstveni problemi koji se odražavaju i na kvalitet njihovog života. Najznačajniju ulogu u formiranju i održavanju

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pravilnog držanja tela imaju mišići, kao aktivan deo aparata za kretanje. Slabost pojedinih mišićnih grupa, njihovo preveliko i jednostrano opterećenje, može da izazove pojavu različitih poremećaja na kičmenom stubu, grudnom košu, gornjim i donjim estremitetima, a posebno na stopalu. Zbog plastičnosti i senzitivnosti dečjeg organizma formiranje pravilnog posturalnog statusa je od posebnog značaja u predškolskom periodu razvoja i u prvim godinama školovanja [2]. Jedan od ključnih perioda za pojavu posturalnih poremećaja predstavlja polazak dece u školu. Deca predškolskog uzrasta većinu vremena u toku dana provode u igri i raznim oblicima kretanja, za razliku od dece mlađeg školskog uzrasta, koja određeno vreme koje su trošili na igru, sada provode u sedećem položaju za vreme trajanja školskih časova (u školi provedu negde oko 97% vremena u sedećem položaju) [3]. Ne treba nikako zaboraviti ni vreme koje provedu u izradi domaćih zadataka, gledanju televizije, korišćenju računara itd. U proseku za oko 50% se smanjuje fizička aktivnost dece u tom periodu [4]. Fizička neaktivnost dovodi do hipotrofije muskulature, smanjenog tonusa mišića, što sve pogoduje, uz nepravilno sedenje, nepravilnom držanju tela pri hodu, razvoju posturalnih telesnih deformiteta i statičkih deformiteta. Deformiteti koštanog sistema dece školskog uzrasta su prateća pojava tokom rasta i razvoja. Najčešće su posledica nepravilnog držanja tela, smanjene fizičke aktivnosti, nepravilnog sedenja, ishrane i niza drugih uzroka [5]. Imajući u vidu da je ovo jedan od kritičnih perioda u toku rasta i razvoja kod dece u kojem postoje velike mogućnosti za pojavu posturalnih poremećaja jer se deca izlažu povećanim fizičkim opterećenjima (npr. nošenje teške školske torbe), potrebno je angažovanje kako roditelja, tako i učitelja i profesora na usmeravanju dece za bavljenje sportom ili bilo kojom fizičkom aktivnošću, kao jedne od važnih preventivnih mera. Mnogi autori su se bavili istraživanjima vezanim za posturalne poremećaje školske dece. Analiza kvantitativnih rezultata istraživanja[2] pokazuje da je veliki broj dečaka i devojčica sa manjim odstupanjima od pravilnog držanja u svim segmentima tela, što govori o velikom broju početnih funkcionalnih oblika deformiteta. U istraživanju posturalnog status dece[6] zaključuje se da grupe ispitanika koje su definisane na osnovu razlika u varijablama za procenu posturalnog statusa grudi, stopala i nogu , imaju statistički značajne razlike u gotovo svim varijablama za procenu motoričkog statusa u korist ispitanika koji nisu imali, ili su imali manje izražene posturalne poremećaje. Razlike u posturalnim poremećajima između devojčica i dečaka uzrasta od 7 do 15 godina uočene su u uzorku ispitanika za uzrast 9-10 godina što autori objašnjavaju činjenicom da devojčice u ovom periodu ulaze u pubertet i samim tim su podložnije nastanku nekih posturalnih poremećaja [7]. Drugi značajan period u kojem se javljaju razlike u posturalnim poremećajima kod dečaka i devojčica je između 11. i 13. godine što autori objašnjavaju periodom završetka puberteta kod devojčica i početkom kod dečaka. Takođe, značajne razlike se beleže i u periodu 12-13. godine kada dečaci ulaze u pubertet. Rezultati istraživanja čiji je cilj bio da se utvrde efekti programiranog rada na status kičmenog stuba osmogodišnje dece Novog Sada, pokazuju da je loše držanje ramena, koje ukazuje na posturalni poremećaj kičmenog stuba u frontalnoj ravni, zastupljeno i kod dečaka i kod devojčica. Uočljive su razlike, međutim one nisu statistički značajne [8,9]. U drugom istraživanju, pak, zaključeno je da je deformitet ravna leđa najmanje zastupljen (4,2%) i prisutan samo kod devojčica. Lordotično loše držanje (51,5%) zastupljeno je najviše kod devojčica [10]. Rezultati drugog istraživanja pokazuju da 34,9% dece ima dobro držanje tela, dok 31,7% ima loše. Lordotično loše držanje je zabeleženo u 12,5% slučajeva, dok je kifotično loše držanje zabeleženo u 16,3% slučajeva [10, 11]. U istraživanju koje je sprovedeno kod dece uzrasta 9 i 10 godina, došlo se do zaključka da je nakon autorizovanog kineziterapijskog programa Thera Band Acadamy koji je trajao 10 meseci, smanjen procenat posturalnih poremećaja kičmenog stuba posle vežbanja i statistički je značajna razlika(p=0,000). Razlika u posturalnom statusu grudnog koša (p=0,479) i stopala (p=0,13) nije statistički značajna u odnosu na inicijalno stanje.

U svom radu [12] dolaze do sledećih rezultata – na uzorku od 1523 učenika od trećeg do šestog razreda osnovnih škola najzastupljeniji poremećaj posturalnog statusa je deformitet stopala - ravna stopala (pedes plana) sa 26,6%, više kod dečaka. Od poremećaja kičmenog stuba, najzastupljenija je skolioza - 19,6%, zatim kifoza – 7,6% i lordoza – 1,0%. Od deformiteta grudnog koša, najzastupljenije su udubljene grudi (pectus excavatus) - 4,2%, češće kod dečaka, u odnosu na ispupčene grudi

(pectus carinatus) – 0,9%. Deformiteti nogu su zastupljeni u 1,9% slučajeva, više kod devojčica. Simov (2011) u svom istraživanju čiji je cilj bio procena posturalnog statusa predškolske dece od 6-7 godina u Leskovcu, zaključuje da su rezultati pokazali da je najveći broj i procenat dece sa spuštenim svodom stopala od I-IV stepena (30,7%). Bez posturalnih poremećaja je 36,1% dece, s jednim deformitetom je 54,5%, a sa dva ili više deformita je 9,3% dece ovog uzrasta[13]. Na uzorku od 434 učenika petog razreda osnovnih škola iz Kragujevca zaključeno je da postoji značajna povezanost telesne visine, sedeće visine tela, kao i telesne mase sa devijacijama kičmenog stuba u lumbalnom delu, izražene u sagitalnoj ravni [14]. Na osnovu ovog istraživanja koje je obuhvatilo 651 učenika oba pola osnovnih škola iz Kragujevca, može se zaključiti da od ukupnog broja ispitanika 87,7% ima pravilne donje ekstremitete, deformitet "X" noge (Genu valgum), ima 7,5%, a deformitet "O" noge (Genu varum) nešto manji procenat (4,7%). Kod ispitanika sa pravilnim donjim ekstremitetima 51,5% ispitanika je muškog pola, a 48,5% je ženskog pola. Deformitet "X" noge je zabeležen kod 53,1% devojčica što je više u odnosu na dečake (46,9%). Deformitet "O" noge je prisutan u 77,4% kod dečaka i zastupljeniji je u odnosu na devojčice (22,6%). Postoji statistički značajna povezanost statusa donjih ekstremiteta, u zavisnosti od pripadnosti polu (P=0,01). Problem istraživanja je da se ustanovi zastupljenost posturalnih poremećaja kod dece mlađeg školskog uzrasta , dok je cilj istraživanja procena posturalnog statusa dece mlađeg školskog uzrasta Osnovne škole "Ivo Lola Ribar" iz Novog Sada.

MATERIJAL I METODE

Uzorak ispitanika predstavlja 61 učenik prvog razreda Osnovne škole "Ivo Lola Ribar" iz Novog Sada - 33 dečaka i 28 devojčica prosečne starosti 8,5 godina. Za procenu posturalnog statusa primenjena je modifikovana vizuelna metoda Napoleona Volanskog. Po ovoj metodi držanje svih segmenata tela ocenjuje se sa 0, 1, 2. Dobro držanje tela ocenjuje sa 0, manje odstupanje sa 1 i veće odstupanje sa 2. Procenjeno je držanja tela u frontalnoj i sagitalnoj ravni.

U frontalnoj ravni, sa zadnje strane tela, posmatran je kičmeni stub u celini, zatim grudna i slabinska krivina. U grudnom delu moguća su odstupanja od pravilnog držanja u levu ili desnu stranu, takođe u slabinskom delu (leva ili desna slabinska skolioza) ili u čitavom kičmenom stubu (totalna skolioza). Takođe, moguća je i kompenzatorna skolioza, odnosno kombinacija grudne i slabinske skolioze [15].

U frontalnoj ravni, sa prednje strane, posmatran je grudni koš. Grebenasto ispučenje grudne kosti iznad nivoa grudnog koša ukazuje na prisustvo deformiteta poznatog kao "kokošije grudi" ili pectus carinatus. Suprotno ovome, udubljenje tela grudne kosti govori o postojanju deformiteta poznatog kao "izdubljene grudi" ili pectus excavatus [16]. Takođe, posmatran je i položaj kolena. Fiziološki ugao koji zaklapaju natkolenice sa potkolenicama iznosi oko 174°, s tim što je on otvoren prema unutra. Ako je taj ugao manji, uočava se pojačan bočni konveksitet kolena, što ukazuje na deformaciju u smislu "O" položaja. Ako je on veći (više od 180°), sa evidentnim bočnim konkavitetom kolena, govorimo o "X" nogama. Ahilove tetive treba da zauzimaju vertikalan položaj u odnosu na petnu kost. Lučno iskrivljenje Ahilovih tetiva prema unutra ukazuje na valgus položaj stopala što je posledica spuštanja uzdužnog svoda stopala. Iskrivljenje Ahilovih tetiva u suprotnom smeru govori o prisustvu izdubljenog stopala [16]. U sagitalnoj ravni procenjeno je držanje vratne, torakalne i slabinske krivine, te posturalni status kolena i stopala. Vratna krivina treba da ima svoje fiziološko zakrivljenje. Povećanje vratne krivine javlja se kao posledica kifotičnog držanja, dok njeno smanjenje ukazuje na ravna leđa i lordotično držanje. Torakalna krivina treba da bude blago zaobljena, a ramena blago pomerena unazad. Njeno fiziološko zakrivljenje treba da iznosi oko 20-35°. Povećanje torakalne krivine iznad 35° ukazuje na kifotično držanje, a njen izostanak na ravna leđa. Fiziološko zakrivljenje slabinske krivine iznosi oko 15 do 30°. Ukoliko je pomenuto zakrivljenje veće i ujedno praćeno povećanim obrtanjem karlice napred i dole (povećana inklinacija) ukazuje na lordotično držanje. Ukoliko postoji odstupanje od pravilnog držanja u oba segmenta, grudnom i slabinskom, u pitanju je kifo-lordotično držanje.

Položaj kolena - natkolenica i potkolenica treba da zauzimaju određeni fiziološki položaj. Prisustvo prekomernog opružanja u kolenom zglobu ukazuje na lordotično držanje ili na deformitet kolenog zgloba, poznatog kao genua recurvate. Položaj stopala - ona treba da zaklapaju prav ugao sa potkolenicom i da imaju jasno izražene svodove.

Spuštanje uzdužnog svoda stopala ukazuje na ravno stopalo (**pes planovalgus**), a prekomerno uzdignut svod, na izdubljeno stopalo (**pes cavus**)[16]. Procena posturalnog statusa je urađena u Osnovnoj školi "Ivo Lola Ribar" u Novom Sadu, u sobi za učitelje koja je svetla, prostrana i topla. Deca su bila minimalno obučena. Merenje je bilo sprovedeno u prepodnevnim časovima, kada su deca imala čas fizičkog vaspitanja. Procenu posturalnog statusa obavili su studenti Fakulteta za sport i fizičko vaspitanje iz Novog Sada. Podaci su obrađeni statističkim programom SPSS for Windows, verzija 17.0. Za utvrđivanje zastupljenosti posturalnih poremećaja i eventualnih razlika po polu korišćena je neparametrijska metoda $\chi 2$ test, na nivou zaključivanja p=0.05

REZULTATI

Rezultati su grupisani i prikazani u tri celine: posturalni poremećaji kičmenog stuba u sagitalnoj ravni, posturalni poremećaji kičmenog stuba u frontalnoj ravni, te posturalni poremećaji grudnog koša, nogu i stopala. Za utvrđivanje frekvencija pojavljivanja posturalnih poremećaja kao i razlika po polu korišćen je $\chi 2$ – test na nivou značajnosti $p \leq 0.05$.

Posturalni poremećaji kičmenog stuba u sagitalnoj ravni odnose se na kifotično, lordotično, kifo-lordotično loše držanje i ravna leđa. Dobro držanje tela procenjeno je ocenom 0, malo odstupanje od normalnog držanja tela procenjivano je sa 1, a znatno odstupanje ocenom 2.

Ispitanici nemaju znatno odstupanje od dobrog držanja tela (ocena 2) kada su u pitanju kifo-lordoza i ravna leđa, a dijagnostikovana su i malo (ocena 1) i znatno (ocena 2) odstupanje od dobrog držanja kod kifotičnog i lordotičnog lošeg držanja tela.

Tabela 1. Brojčana i procentualna vrednost zastupljenosti posturalnih poremećaja kičmenog stuba u sagitalnoj ravni ukupnog uzorka ispitanika
Table 1. Number and percentage value of postural disorders of the spinal column in the sagittal level of the total sample of subject

Varijabla	Ocena	Broj			% U odnosu na posturu			% U odnosu na grupu			% Ukupno			χ^2	p
		M	Ž	Σ	M	Ž	Σ	M	Ž	Σ	M	Ž	Σ		
Kifotično loše držanje	0	26	25	51	51	49	100	78.8	89.3	83.6	42.6	41	83.6		
	1	5	2	7	71.4	28.6	100,0	15.2	7.1	11.5	8.2	3.3	11.5	1,237	0,539
	2	2	1	3	66.7	33.3	100,0	6.1	3.6	4.9	3.3	1.6	4.9		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54.1	45.9	100,0		
Lordotično loše držanje	0	13	15	28	46.4	53.6	100,0	39.4	53.6	45.9	21.3	24.6	45.9		
	1	16	9	25	64	36	100,0	48.5	32.1	41	26.2	14.8	41	1,704	0,426
	2	4	4	8	50	50	100,0	12.1	14.3	13.1	6.6	6.6	13.1		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54.1	45.9	100,0		
Kifo-lordotično držanje	0	28	26	54	51.9	48.1	100,0	84.8	92.9	88.5	45.9	42.6	88.5		
	1	5	2	7	71.4	28.6	100,0	15.2	7.1	11.5	8.2	3.3	11.5	0,956	0,328
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54.1	45.9	100,0		
Ravna leđa	0	32	23	56	58.2	41.8	100,0	97	82.1	90.2	52.5	37.7	90.2		
	1	1	2	6	16.7	83.3	100,0	3	17.9	9.8	1.6	8.2	9.8	3,755	0,650
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54.1	45.9	100,0		

Tabela 2. Brojčana i procentualna vrednost zastupljenosti posturalnih poremećaja kičmenog stuba u frontalnoj ravni ukupnog uzorka ispitanika
Table 2. Number and percentage value of postural disorder representation spinal column at the frontal level of the total sample of subjects

Varijabla	Ocena	Broj			% U odnosu na posturu			% U odnosu na pol			% Ukupno			χ^2	p
		M	Ž	Σ	M	Ž	Σ	M	Ž	Σ	M	Ž	Σ		
Leva grudna skolioza	0	26	23	49	53.1	49.9	100,0	78.8	82.1	80.3	42.6	37.7	80.3	1,603	0,449
	1	7	4	11	63.6	36.4	100,0	21.2	14.3	18	11.5	6.6	18		
	2	0	1	1	0	100	100,0	0	3.6	1.6	0	1.6	1.6		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54.1	45.9	100,0		
Desna grudna skolioza	0	24	20	44	54.5	45.5	100,0	72.7	71.4	72.1	39.3	32.8	72.1	4,678	0,096
	1	5	8	13	38.5	61.5	100,0	15.2	28.6	21.3	8.2	13.1	21.3		
	2	4	0	4	100	0	100,0	12.1	0	6.6	6.6	0	6.6		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	0	100,0	54.1	45.9	100,0		
Leva slabinska skolioza	0	30	25	55	50	50	100,0	90.9	89.3	90.2	49.2	41	90.2	0,045	0,832
	1	3	3	6	54.1	45.9	100,0	9.1	10.7	9.8	4.9	4.9	9.8		
	Ukupno	33	28	61	52,6	47,4	100,0	100,0	0	100,0	54.4	45.9	100,0		
Desna slabinska skolioza	0	33	26	59	55.9	44.1	100,0	100,0	92.9	96.7	54.1	42.6	96.7	2,437	0,118
	1	0	2	2	0	100	100,0	0	7.1	3.3	0	3.3	3.3		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	0	100,0	54.1	45.9	100,0		
Leva totalna skolioza	0	31	26	57	51,4	45.6	100,0	93.9	92.9	93.4	50.8	42.6	93.4	0,29	0,865
	1	2	2	50	50	37,5	100,0	6.1	7.1	6.6	3.3	3.3	6.6		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	0	100,0	54.1	45.9	100,0		

Tabela 3. Brojčana i procentualna vrednost zastupljenosti posturalnih poremećaja grudnog koša ukupnog uzorka ispitanika.
Table 3. Number and percentage value of postural thoracic disorders of the total sample of respondents

Varijabla	Ocena	Broj			% U odnosu na posturu			% U odnosu na pol			% Ukupno			χ^2	p
		M	Ž	Σ	M	Ž	Σ	M	Ž	Σ	M	Ž	Σ		
Izdubljene grudi	0	29	22	51	56,9	43,1	100,0	87,9	78,6	83,6	45,7	36,1	83,6	1,637	0,433
	1	4	5	9	44,4	55,6	100,0	12,1	17,9	14,8	6,6	8,2	14,8		
	2	0	1	1	0	100	100,0	0	3.6	1.6	0	1,6	1,6		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54,1	45,9	100,0		
Ispupčene grudi	0	31	27	58	53,4	46,6	100,0	93,9	96,4	95,1	50,8	44,3	95,1	0,201	0,654
	1	52	1	3	66,7	33,3	100,0	6,1	3,6	4,9	3,3	1,6	1,6		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	0	100,0	54,1	45,9	100,0		
Ravne grudi	0	31	25	56	55,4	44,6	100,0	93,9	89,3	91,8	50,8	41	91,8	0,436	0,509
	1	2	3	5	40	60	100,0	6,1	10,7	8,2	3,3	4.9	8,2		
	Ukupno	33	28	61	54,1	45,9	100,0	100,0	0	100,0	54,1	45,9	100,0		

Tabela 4. Brojčana i procentualna vrednost zastupljenosti posturalnih poremećaja nogu i stopala ukupnog uzorka
Table 4. Number and percentage value of postural leg disorder and foot of the total sample.

Varijabla	Ocena	Broj			% U odnosu na posturu			% U odnosu na pol			% Ukupno			χ^2	p
		M	Ž	Σ	M	Ž	Σ	M	Ž	Σ	M	Ž	Σ		
„ X" noge	0	26	24	50	52	48	100,0	78,8	85,7	82	42,6	39,3	82	0,492	0,483
	1	7	4	11	63,6	36,4	100,0	21,2	14,3	18	11,5	6,6	18		
	Ukupno	33	28	61	54.1	45.9	100,0	100,0	100,0	100,0	54,1	45,9	100,0		
„ O" noge	0	32	27	59	54,2	45,8	100,0	97	96,4	96,7	52,5	44,3	96,7	0,14	0,906
	1	1	1	2	50	50	100,0	3	3,6	3,3	1,6	1,6	3,3		
	Ukupno	33	28	61	54,1	45.9	100,0	100,0	100,0	100,0	54,1	45,9	100,0		
Hiperekstenzija nogu	0	33	25	58	56,9	43,1	100,0	100,0	89,3	95,1	54,1	41	95,1	3,719	0,054
	1	0	3	3	0	100,0	100,0	0	10,7	4,9	0	4,9	4,9		
	Ukupno	33	28	61	54,1	45,9	100,0	100,0	100,0	100,0	54,1	45,9	100,0		
Ravna stopala	0	8	5	13	61,5	38,5	100,0	24,2	17,9	21,3	13,1	82	21,3	0,620	0,733
	1	18	18	36	50	50	100,0	54,5	64,3	59	29,5	29,5	59		
	2	7	5	12	58,3	41,7	100,0	21,2	17,9	19,7	11,5	8,2	19,7		
	Ukupno	33	28	61	54,1	45,9	100,0	100,0	100,0	100,0	54,1	45,9	100,0		

DISKUSIJA

Ono što se može zaključiti na osnovu ovog istraživanja jesta da je zastupljenost kifoze sa većim uglom od 40°, koja se smatra patološkom[17] u školskoj populaciji uzrasta od 10 do 17 godina zabeležen je u većem procentu kod dečaka (15,3%) u odnosu na devojčice (12%). Bez obzira što se radi o starijem uzrastu u odnosu na ispitivanu populaciju u našem istraživanju, može se zaključiti da su dečaci izloženiji pojavi ovog posturalnog poremećaja po rezultatima našeg istraživanja, koji u kasnijem uzrastu može da preraste u deformitet. Rezultati ovog istraživanja poklapaju se sa rezultatima istraživanja (Jovović i saradnici, 2006), koji su ispitivali učestalost krilastih lopatica kod školske dece Nikšića. Ako znamo da krilaste lopatice ukazuju na kifotično loše držanje, onda ovo podudarnje rezultata ima smisla. Naime, ustanovljeno je da se kod ispitanika muškog pola krilaste lopatice javljaju u 74,6% slučajeva što je znatno više u odnosu na ispitanice (43,9% slučajeva). Upoređujući rezultate sa istraživanjem Bogdanovića i saradnika [14] uočljivo je da se i ovi rezultati podudaraju jer ne postoji statistički značajna razlika u statusu kičmenog stuba u sagitalnoj ravni između ispitanika muškog i ženskog pola. Lordotično loše držanje zastupljeno je u većem procentu kod ispitanica (61,3%) u odnosu na ispitanike muškog pola (38,7%), ali ni ove razlike nisu statistički značajne (p= 0.724). Rezultati drugog istraživanja [15] sprovedenog sa ciljem da se utvrdi zastupljenost posturalnih poremećaja kod dece uzrasta 12-13 godina u odnosu na indeks telesne mase, kao i eventualne razlike po polu, ukazuju na veću zastupljenost lordotičnog držanja kod devojčica nego kod dečaka. Razlika u tipu držanja tela između dečaka i devojčica u ovom istraživanju nije statistički **visoko** značajna (p= 0.023) na nivou zaključivanja p=0.00, ali jeste na nivou p=0,05 veći procenat devojčica sa lordotičnim držanjem u odnosu na dečake [15] što se poklapa sa rezultatima u ovom istraživanju. Takođe ispitanici muškog pola imaju bolji status kičmenog stuba u sagitalnoj ravni [8] u odnosu na ispitanice koje imaju lošije držanje u slabinskom delu kičmenog stuba od dečaka (lordotično držanje), ali ni ove razlike nisu statistički značajne (p = 0.128), što se slaže sa rezultatima našeg istraživanja. Što se tiče kifo-

lordoze, devojčice imaju bolji posturalni status iako on nije statistički značajan ($\chi 2 = 0.956$; $p = 0.328$). Rezultati istraživanja se poklapaju sa rezultatima istraživanja [9] koji ukazuju na takođe veću učestalost pojave kifo-lordotičnog držanja kod dečaka (45,5%) u odnosu na devojčice (32,2%), a razlike takođe nisu statistički značajne ($p= 0.465$). Upoređujući rezultate ovog istraživanja koji se odnose na posturalne poremećaje u sagitalnoj i frontalnoj ravni kičmenog stuba u ukupnom uzorku ispitanika sa rezultatima istraživanja[7, 8], bez obzira na veličinu uzorka ispitanika, možemo zaključiti da se poklapaju, jer u ovom uzrastu nema statistički značajne razlike u odnosu na polni dimorfizam. Autori opravdavaju činjenicom da ni dečaci ni devojčice još nisu ušli u pubertet kao kritični period u rastu i razvoju dece za koji je karakteristična pojava posturalnih poremećaja. Rezultati istraživanja dobijeni na osmogodišnjoj deci Novog Sada [10] pokazuju da ne postoji statistički značajna razlika u statusu frontalne ravni kičmenog stuba u odnosu na polni dimorfizam što se poklapa i sa rezultatima ovog istraživanja. Rezultati ovog istraživanja su slični rezultatima istraživanja [13] u kojem je takođe konstatovana veća zastupljenost poremećaja „ X“ noge u odnosu na „ O“ noge. Međutim, rezultati se ne poklapaju u pogledu zastupljenosti poremećaja po polu. U navedenom istraživanju veći je procenat devojčica sa „ X“ nogama i veći postotak dečaka sa „ O“ nogama, što se ne slaže sa našim istraživanjem. Nepodudarnost možemo naći u različitoj veličini ispitivanih uzoraka, kao i različitoj uzrasnoj kategoriji. Rezultati dobijeni u ovom istraživanju u pogledu zastupljenosti ravnih stopala prema polnom dimorfizmu se razlikuju od rezultata istraživanja [15] u kome je veći postotak ispitanika muškog pola sa blagim odstupanjem od dobrog položaja u odnosu na ispitanice. Značaj ovog istraživanja ima za cilj da naglasi ono što je već više puta dokazivano, a to je da je period u rastu i razvoju dece od 7 - 8 godina izuzetno kritičan, zbog mogućnosti pojave posutralnih poremećaja. Neophodna je, kako za preventivu, tako i za otklanjanje telesnih deformiteta, veća fizička aktivnost i uključivanje programa korektivne gimnastike u redovne školske aktivnosti pod nadzorom stručnih lica. Naravno, ključnu ulogu u svemu tome treba da preuzmu roditelji, učitelji, nastavnici i profesori fizičkog vaspitanja, ali i školski lekari i pedijatri te ostali stručni kadrovi i javnost uopšte.

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AKUTNA RESPIRATORNA INSUFICIJENCIJA UZROKOVANA PAPILOMATOZOM LARINGSA

ACUTE RESPIRATORY INSUFFICIENCY CAUSED BY LARYNGEAL PAPILLOMATOSIS

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Sažetak: Rekurentna respiratorna papilomatoza je retka bolest, najčešće lokalizovana u laringsu. Prevalenca je 1-4 obolelih na 100 000. Najčešće počinje u ranom detinjstvu i karakteriše je hronični, recidivantni i nepredvidiv tok. Humani papiloma virus tipovi 6 i 11 je uzročnik bolesti koja se manifestuje postepenim razvojem promuklosti, vizinga, hrkanja, dispnejom i osećajem stranog tela u guši. Prikazujemo kliničku sliku akutne respiratorne insuficijencije uzrokovane rekurentnom respiratornom papilomatozom, u martu 2017. godine kada je kod pacijenta došlo do naglog gušenja, cijanoze, ispiratornog stridora i borbe za vazduh. Učinjena je urgentna traheotomija i plasiran armirani tubus br 7 jer se nije imao uvid u nivo opstrukcije na potezu larings-račva traheje. Hospitalizovan je u jedinici intenzivnog lečenja, obezbeđenog vazdušnog puta i dobre saturacije. U uslovima opšte anestezije bronhoskopski fleksibilnim bronhoskopom odstranjen sluzavo-gnojni čep iz traheje, potom neposredno ispod otvora traheostome celom cirkumferencijom lumena viđene papilomatozne formacije koje lumen svode na 15%. Učinjena je konsekutivna mehanička rekanalizacija rigidnim tubusima sa ektrakcijom papiloma forcepsom. Nakon intervencije traheja je prolazna na oko 90% lumena. Pacijent potom stabilan, ubrzo otpušten, javljao se na kontrolnu bronhoskopiju nakon mesec dana kada je nalaz bio zadovoljavajući. Ovo je njegova 55. hospitalizacija zbog osnovne bolesti. Ponavljane traheotomije nose rizik od širenja virusne infekcije u traheju i pluća, ali su nekada neizbežne zbog neočekivane životne ugroženosti obolelih od papilomatoze laringsa.
Ključne reči: rekurentna laringealna papilomatoza, humani papiloma virus, larings, traheotomija.

Summary: Recurrent respiratory papillomatosis is a rare disease, most commonly localized in the larynx. The prevalence is 1-4 diseased in every 100 000 people. It often starts in early childhood and is characterized by a chronic, recurrent and unpredictable development. Human papilloma virus type 6 and 11 is the cause of a disease that manifests itself with gradual development of hoarseness, vising, snoring dyspnea and a feeling of a strange body in the throat. A clinical picture of an acute respiratory insufficiency is shown, caused by recurrent respiratory papillomatosis. In March 2017. when the patient had experienced sudden choking, cyanosis, inspiratory stridor and trouble breathing. an urgent tracheotomy was conducted and tube no. 7 was reinforced in order to determine the level of obstruction from the larynx to the trachea. The patient was hospitalized in the department for intensive care, with an ensured airway and good saturation. Under anesthesia, a flexible bronchoscopy was used to remove a mucous cap from the trachea, after which a papillomatosis formation was seen at the entrance of the tracheostomy over the entire circumference of the lumen, which decreased the lumen to 15%. A consecutive mechanical recanalization was done with rigid tubes with the extraction of the papilloma with forceps. After the intervention, the trachea became transient up to 90% of the lumen. Patient is afterwards stable, soon released and has appeared for a checkup a month later, with satisfying results. This was his 55th hospitalization because of the primary disease. Repetition of tracheotomy increases the risk of

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spreading the infection into the trachea and lungs but is sometimes necessary due to unexpected life threatening situations in those suffering from papillomatosis in the larynx.
Key words: recurrent laryngeal papillomatosis, human papillomavirus, larynx, tracheotomy.

UVOD

Rekurentna respiratorna papilomatoza (RRP) je redak entitet i pacijenti mogu imati tegobe i mesecima pre nego što se bolest otkrije. Uzrokuje je humani papilloma virus (HPV) [1]. Prevalenca bolesti je različita u zavisnosti od godina starosti kada se prezentuje, države i socioekonomskog statusa pacijenata uključenih u statističke analize, pa je generalno prihvaćeno da je 1-4 obolelih na 100 000 [2]. S obzirom da je najčešće lokalizovana u laringsu, simptomi gornjih disajnih puteva su predominantni [3]. Promuklost je najčešći simptom, slede promena boje glasa, osećaj prisustva stranog tela u grlu, gušenje, dispneja i inspiratorni vizing [3]. Nekada akutna respiratorna insuficijencija može biti prvi simtom bolesti. Vrlo retko (1%), na terenu RRP, može se razviti skvamocelularni karcinom [4,5]. U tom slučaju HPV 16 i 18 su odgovorni za metaplaziju [6].

PRIKAZ BOLESNIKA

Pacijent starosti 57. godina, od svog šestog meseca života boluje od rekurentne respiratorne papilomatoze. Iz lične anamneze znamo da je bolest otkrivena u ranom detinjstvu jer je bilo tegoba sa disanjem, kašlja i inspiratornog vizinga. Inicijalna dijagnostička laringoskopija je učinjena 1961. godine, u njegovoj prvoj godini života i tada je prvi put operativno rešena papilomatoza. Od tada je ukupno 55 puta hospitalizovan na Klinici za Otorinolaringologiju u Beogradu. Tri puta je rađena traheotomija. Rekanalizacija središnog dela traheje u dužini 2 cm učinjena je 2010. godine.. Redovno se javlja na kontrolne preglede. Inače dobrog opšteg zdravlja, nepušač, aktivan, boluje od hipertenzije koju leči redovnim uzimanjem antihipertenzivne terapije.

Prikazujemo kliničku sliku akutne respiratorne insuficijencije kod njega, u martu 2017. godine kada je došlo do naglog gušenja, cijanoze, ispiratornog stridora i borbe za vazduh. Učinjena je urgentna traheotomija i plasiran armirani tubus br. 7. jer se nije imao uvid u nivo opstrukcije na potezu larings-račva traheje. Hospitalizovan je u jedinici intenzivnog lečenja, obezbeđenog vazdušnog puta i dobre saturacije. Na prijemu je bio svestan, budan, acijanotičan, eupnoičan u miru, komunikativan. Auskultatorno diskretno oslabljen disajni šum, vizing obostrano pri bazama, izraženije desno. Srčana akcija ritmična, tonovi jasni, tenzija 170/100, srčana frekvenca 122/min. Laboratorijske analize:

Le- $14x10^9$/L, Er- $5,0x10^{12}$/L, Hgb- 152g/L, Hct- 45%, SE- 12/sat, Glikoza- 7mmol/L, CRP- 65 mg/L, pH= 7,52, pCO_2 - 5,3kPa, pO_2 -7,2 kPa. Fiberlaringoskopom je konstatovana uredna pokretljivost laringsa, bez vidljivih izraštaja u njemu, početnom delu traheje sve do nivoa traheostome. S obzirom na nivo opstrukcije, sa Klinike za otorinolaringologiju je premešten na Kliniku za pulmologiju. U jutarnjim satima kod njega dolazi do pojave stridoroznog disanja kada je u uslovima opšte anestezije bronhoskopski fleksibilnim bronhoskopom odstranjen sluzavo-gnojni čep iz traheje, potom neposredno ispod otvora traheostome celom cirkumferencijom lumena viđene su papilomatozne formacije koje lumen svode na 15%. Učinjena je konsekutivna mehanička rekanalizacija rigidnim tubusima sa ektrakcijom papiloma forcepsom. Nakon intervencije traheja je prolazna na oko 90% lumena. Pacijent medikamentno lečen antibioticima, antikoagulansima, oksigenoterapijom i redovnom internističkom terapijom. Nakon intervencije stabilan, ubrzo otpušten, javljao se na kontrolnu bronhoskopiju nakon mesec dana, kada je nalaz bio zadovoljavajući.

DISKUSIJA

Najčešći tipovi HPV koji su identifikovani u respiratornim papilomima su tipovi 6 i 11 (90%) [7]. HPV 11 nalazimo u 50-100% uzoraka i on ima agresivniji tok [8]. Simptomi bolesti se uobičajeno ne javljaju u prvih šest meseci života i tegobe počinju kako papilomi rastu [9]. Kada se bolest javi u detinjstvu možemo očekivati da papilomi nastave sa rastom i u tinejdžerskim godinama [10]. U podacima iz literature nalazimo oprečne stavove o težoj formi respiratorne papilomatoze

povezane sa HPV 11 tipom virusa. Neke studije potvrđuju tu vezu dok u drugima nije uočena povezanost sa infekcijom ovim tipom virusa i težom kliničkom slikom bolesti [11].

Klinički tok bolesti je promenljiv i nepredvidiv. U nekim slučajevima bolest je prisutna ali stabilna, sa jednom do dve hirurške intervencije godišnje i spontanim remisijama. Kod ostalih dobija agresivniji tok, sa intenzivnim rastom papiloma i čestim intervencijama [12]. Periodi remisije su vrlo individualni, mogući su u svakom periodu bolesti i opravdano se mogu očekivati kada je bolest ograničena na larings.

Osnovni terapijski protokol je hirurško odstranjivanje polipa i skoriji napredak fleksibilnih laringoskopa i laserske tehnike omogućava povratak na ambulantne procedure kako su ranije rešavani papilomi, pre intervencija u opštoj anesteziji [3]. Standardni terapijski pristup je CO2 laser. Fotoangiolitički laseri novije generacije funkcionišu tako što oksihemoglobin apsorbuje svetlosnu energiju. Oni vrše selektivnu fotokoagulaciju krvnih sudova papiloma dok pritom čuvaju epitel i prave minimalno termalno oštećenje okolnog tkiva. Nisu zabeležene adhezije prednje komisure nakon fotoangiolitičkog laserskog tretmana [3,13].

Među hirurškim intervencijama uključena je i traheotomija, rezervisana za agresivnije slučajeve kada su kompromitovani vazdušni putevi i nakon neuspešnih pokušaja odstranjenja papiloma. Kada je traheotomija neizbežna, treba je razmotriti što ranije, odnosno dok je tok bolesti pod kontrolom i dok se vazdušni putevi čine stabilnim jer traheotomija predstavlja cevovod za distalno širenje bolesti i novu kolonizaciju virusa po traheobronhijalnom stablu [14]. U retrospektivnoj studiji Korle-Bu kumulativni broj traheotomija iznosi 14,5% kod obolelih od RRP pri čemu je kod pojedinih pacijenata izvođena više puta. Broj traheotomija raste sa povećanjem broja hirurških intervencija kod obolelih [15].

Dopunski terapijski protokoli se razvijaju jer su hirurške ablacije često agresivne a nedovoljne da spreče recidive. O njima treba razmišljati kod pacijenata kod kojih postoje više od četiri intervencije godišnje [12].

Cidofovir, kao inhibitor virusne DNK polimeraze uzrokuje apoptozu ćelije zaražene, između ostalih i HPV virusom, i koristi se u svetu od 1998. godine. Rezultati pokazuju dugoročni koristan efekat terapijske primene u poređenju sa minimalnim neželjenim sporednim efektima. Još uvek traju diskusije u Evropskom udruženju laringologa o efikasnosti i eventualnim neželjenim efektima ovog leka. Kod RRP se aplikuje kao sublezijalna injekcija [1,16,17,18].

Bevacizumab je monoklonsko antitelo koje inhibiše endotelijalni faktor rasta i ima antiangiogenetski efekat. U kombinaciji sa fotoangiolitičkim laserom ima sinergistički efekat. Studije na deci sa laringealnom papilomatozom su pokazale da je lokalna aplikacija bevacizumaba (1.25-2.5 mg/ml) smanjila broj hirurških intervencija i poboljšala kvalitet života [19,20]. Kohortna studija u kojoj su se lokalno koristile visoke doze bevacizumaba nije pokazala lokalne i sistemske neželjene efekte ovog leka [21].

Novi terapijski pristupi su usmereni na inhibitore receptora epidermalnog faktora rasta, faktore proapoptoze, stimulatore urođenog i stečenog imunog odgovora i rekombinantne DNK vaccine [22]. Istražuju se efekti indol-3-karbinola, retinoinska kiselina i antirefluksna terapija cimetidinom.

Interesantna su iskustva sa četvorovalentnom vakcinom protiv HPV virusa tipovi 6, 11, 16 i 18 čijom se primenom smanjuje incidence RRP, a kod pacijenata koji već boluju od te bolesti dolazi do snižavanja titra antitela protiv HPV virusa, produžava se period između hirurških intervencija, a kod 40% obolelih dolazi do remisije bolesti [23,24]. Dalja istraživanja u tom pravcu se očekuju. Kod vakcinacije, antitela prolaze uteroplacentnu barijeru i novorođenčad su imuna na HPV [25].

ZAKLJUČAK

Kod pacijenata sa disfunkcijom glasa i promuklošću treba misliti na moguću infekciju HPV. Ukoliko se dijagnostikuje bolest, imati na umu nepredvidiv tok bolesti koji može dovesti do akutne respiratorne insuficijencije.

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KOMPARACIJA TRI SLUČAJA SEKUNDARNOG TIPA ATRIJALNOG SEPTALNOG DEFEKTA

COMPARISON OF THREE CASES OF SECUNDUM ATRIAL SEPTAL DEFECT

Gordana Đorđević

DEČIJE ODELJENJE, DOM ZDRAVLJA NIŠ,

Sažetak: Sekundarni tip atrijalnog septalnog defekta (ASDs) je jedna od najčešćih kongenitalnih srčanih anomalija. Etiologija ASD je multifaktorijalna; određene mutacije gena, ili lekovi ili bolest majke mogu dovesti do poremećaja u razvoju srca i pojave ASD. On se može javiti kao izolovana anomalija ili u sklopu određenih sindroma. Dijagnoza se najčešće postavlja ultrazvučnim nalazom na rođenju, ali i u prvim mesecima ili godinama života. Češće se javlja kod ženskog pola. Veličina defekta može biti različita (od 1mm do 25 mm i više). Najveći broj defekata se spontano zatvori. Cilj rada je bio da se prikažu tri slučaja ASDs kod dece različitog uzrasta kada je defekt dijagnostikovan i sa različitim tokom zatvaranja. Za rad su korišćeni podaci iz zdravstvenih kartona, nalazi ehokardiografije i elektrokardiograma. Veličina defekta kod ove dece se kretala od 4,5–7 mm. Kod dva deteta ASDs se spontano zatvorio, dok se kod jedne devojčice defekt povećavao sa uzrastom te je bila indikovana hirurška intervencija.Tok zatvaranja ASD ne može se sa sigurnošću predvideti na osnovu veličine defekta u trenutku dijagnostikovanja. Zato je neophodno redovno praćenje, kako bi se sprečile moguće komplikacije.
Ključne reči: atrijalni septalni defekt, sekundarni tip, tok zatvaranja, ambulantna pedijatrijska praksa.

Summary: The secundum atrial septal defect (ASDs) is the most common congenital cardiac anomaly. The etiology is multifactorial; the certain gene mutations, some medicaments or mother´s diseases may lead to the disorder in cardiac development and the occurrence of the ASD. It could occur as an isolated anomaly or within certain syndromes. The diagnosis is most often established by echocardiography findings at birth, but also in the first months or years of life. It more often occurs in the female gender. Defect size may vary (from 1mm to 25 mm and more). The majority of them closes spontaneously. The aim of the paper was to present three cases of ASDs in children of different ages when the defects were diagnosed, and with different course of closing. Medical records, echocardiogram and electrocardiogram have been used. The size of the defects with these children ranged from 4.5–7 mm. ASDs spontaneously closed in two cases, while in once the defect increased in size with age, and surgery was indicated. The course of ASD closing based on the size of the defect at the time of diagnosis, cannot be predicted with absolute certainty, and because of that regular monitoring is required in order to prevent possible complications.
Key words: secundum atrial septal defect, secundum type of septal atrial defect/course of closing, echocardiography, outpatient pediatric practice

UVOD

Poremećaji u razvoju srčanih struktura spadaju u najčešće razvojne greške [1], a među njima je najčešći poremećaj pretkomorske septacije — atrijalni septalni defekt (ASD). Smatra se da je ASD zastupljen u oko 10% slučajeva svih kongenitalnih srčanih anomalija [2–6]. Prema delu interatrijalnog septuma gde je defekt pozicioniran, ASD se deli u četiri tipa: ASD secundum, ASD primum, sinus venosus ASD i sinus coronarius ASD. ASD secundum je najzastupljeniji [7, 8] I češći je kod ženskog pola [7–10]. Smatra se da se pretkomorska septacija dešava u periodu od kraja 6. nedelje gestacije [ekvivalentno Carnegie stadijumu (CS) 14)] do 8. nedelje gestacije (ekvivalentno CS 18) [11]. Međupretkomorna pregrada se formira od dve srpaste membrane, imenovane kao septum primum i septum secundum. Ove dve membrane se međusobno spajaju ostavljajući mali otvor –

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foramen ovale (FO), putem koga se ostvaruje komunikacija između dve pretkomore u toku fetalnog života [5, 11, 12]. Etiologija nastanka ASD je multifaktorijalna; navedeni su defekt srčanih transkripcionih faktora, mutacija ciljnih gena ili izloženost majke rizicima okruženja [1, 4, 13]. Sve je više podataka da dejstvo lekova, poput talidomida, vitamina A, indometacina, ili bolest majke (rubela, influenca, fenilketonurija, pregestacioni dijabetes) predstavljaju faktore rizika za nastanak urođenih srčanih defekata [14]. ASD se može javiti kao izolovani poremećaj u srčanom razvoju – nesindromski (sporadični) ili u sklopu sindroma sa dokazanim genetskim promenama (Alagille-, Noonan-, Holt-Oram- i drugi sindromi) [1, 13]. Dijagnostikovanje ASD je najčešće u dečijem uzrastu, odnosno tokom rutinske pedijatrijske prakse. Dokazuje se ehokardiografski Kolor Doppler ultrazvučnim nalazom [8], a dopunske informacije mogu se dobiti i putem magnetne rezonance i kompjuterizovane tomografije [7]. Elektrokardiogram nije pouzdana metoda za skrining ASD [15]. Defekti međupretkomornog septuma mogu biti različite veličine; opisani su mali (< 3 mm), ili veoma veliki (≥ 25 mm) [16]. Kroz defekt se odvija protok krvi od leve ka desnoj pretkomori uslovljavajući tako levo-desni shunt [5, 7]. Podaci o procentu spontanog zatvaranja ASD su različiti; opisan je procenat od 25,6% [9] pa do 92% [8]. Prema istraživanjima, defekti manje veličine se u većem procentu spontano zatvaraju, dok veliki defekti u najvećem procentu zahtevaju hiruršku korekciju [8, 9]. Komplikacije nezatvorenog ASD mogu biti u vidu pulmonalne hipertenzije, volumenskog opterećenja desne pretkomore i desne komore, kardiomegalije, atrijalne aritmije, zastoja u rastu, paradoksalne embolizacije ili kongestivne srčane insuficijencije [2, 5, 7–9, 15].

Cilj ovog rada je bio da se prikažu tri slučaja sekundarnog ASD kod dece različitog uzrasta kada je defekt dijagnostikovan, kao i sa drugačijim tokom zatvaranja.

MATERIJAL I METODE

Za ovaj rad korišćeni su podaci iz zdravstvenih kartona pacijenata i izveštaji o obavljenim dijagnostičkim procedurama. Iz otpusnih listi na rođenju, zdravstvenih kartona i ultrazvučnih nalaza pacijenata utvrđeno je vreme dijagnostikovanja, veličina i promena veličine ASDs.

Analizirani su sledeći parametri: uzrast deteta kada je dijagnostikovan defekt, veličina defekta u trenutku dijagnostikovanja, pol deteta, EKG nalaz, postojanje uvećanja desne pretkomore i uzrast deteta kada je defekt zatvoren.

REZULTATI

Od oko 2000 pacijenata čije podatke poseduje autor kao izabrani pedijatar, petnaestoro dece(oko 0,75%) je imalo dijagnostikovan ASD (devetoro dece je imalo sekundarni ASD kao izolovanu srčanu manu a šestoro dece je imalo ASD sa pridruženim srčanim anomalijama). Odnos polova dece sa sekundarnim ASD je 6:3 u korist devojčica. Izdvojena su tri slučaja sa različitom dimenzijom defekta u vreme postavljanja dijagnoze, različitim tokom i vremenom zatvaranja.
Izabrana tri od devet slučajeva (3/9) u evidenciji izabranog pedijatra o pacijentima sa sekundarnim ASD prikazana su u Tabeli 1.

Slučaj 1 se odnosi na prevremeno rođenu devojčicu, telesne težine 1750 g. Sekundarni ASD, veličine 7 mm, bio je dijagnostikovan na rođenju, istovremeno sa opterećenjem i uvećanjem desne pretkomore. Takođe su bile dijagnostikovane ingvinalna i umbilikalna hernija. Defekt se spontano zatvorio u 20. mesecu života.

Slučaj 2 se odnosi na dečaka iz prevremeno završene blizanačke monozigotne trudnoće, telesne težine na rođenju 1800 g. Udružena anomalija — ingvinalna hernija, takođe je bila evidentirana. U uzrastu od 1,5 meseca utvrđeno je postojanje sekundarnog ASD, veličine 4,5 mm uz istovremeno uvećanje desne pretkomore i umereno povećan pritisak plućne cirkulacije; elektrokardiogramski nalaz je ukazivao na inkompletni blok desne grane. Brat blizanac nije imao ASD, niti udružene anomalije. Oba dečaka su imala strabizam. Defekt se spontano zatvorio u uzrastu od 6 godina.

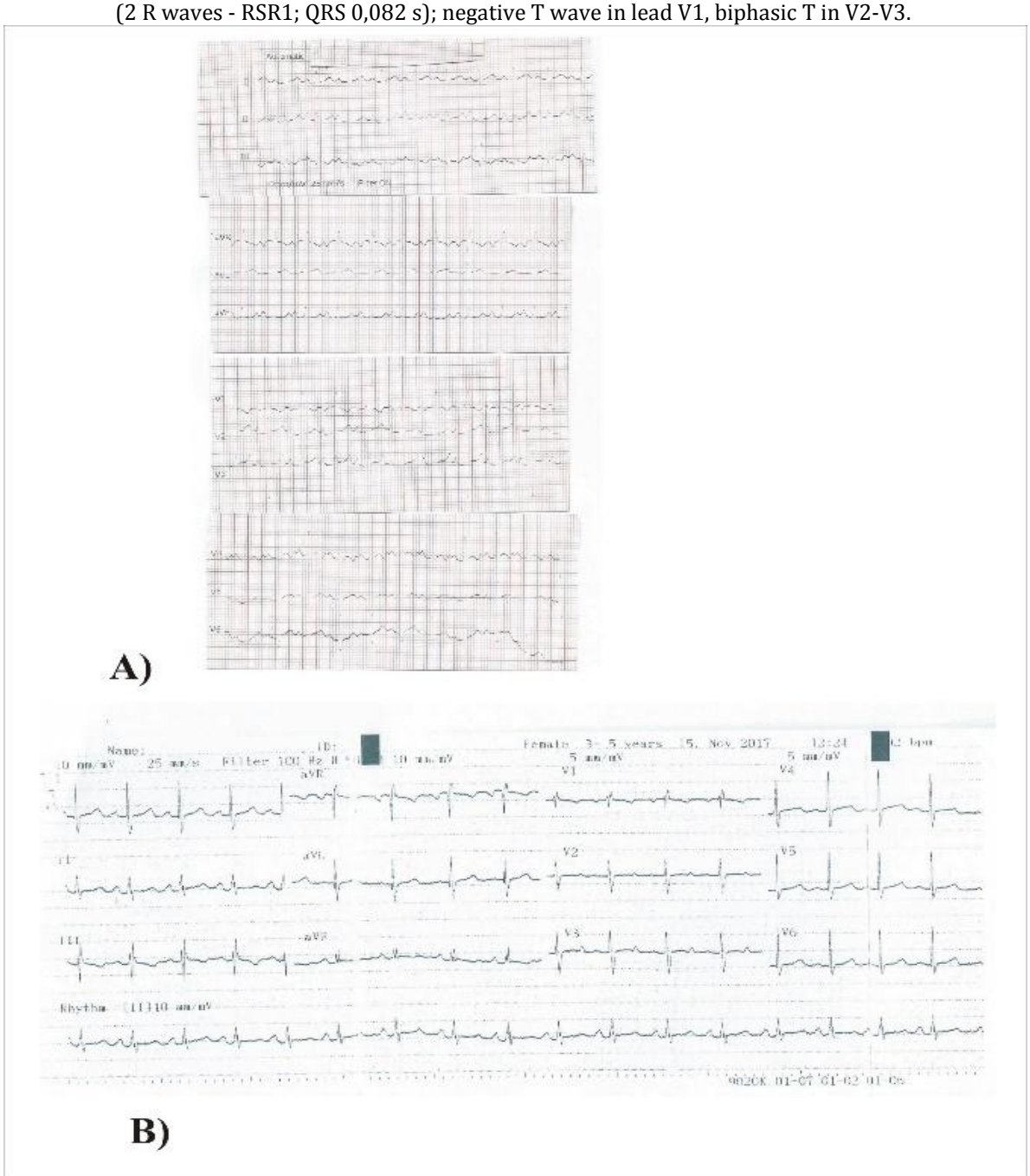
Tabela 1. Komparacija istraživanih parametara kod tri slučaja sa sekundarnim atrijalnim septalnim defektom.
Table 1 Comparison of investigated parameters in three cases with a secundum atrial septal defect.

Slučaj	Pol	Uzrast kada je postavljena dijagnoza	Dimenzije defekta pri postavljanju dijagnoze	Nalaz elektrokardiograma u vreme postavljanja dijagnoze	Uvećanje desne pretkomore	Tok defekta (spontano zatvaranje ili hirurška korekcija)	Udružena patologija
1	Ž	Na rođenju	7 mm	Bez podataka	da	Spontano zatvoren do uzrasta 20 mes.	Hernia ingvinalis; Hernia umbilicalis
2	M	1,5 mesec	4,5 mm	Inkompletni blok desne grane	da	Spontano zatvoren u uzrastu od 6 god.	Hernia ingvinalis
3	Ž	21 mesec	5,5 mm	AV blok I stepena; Inkompletni blok desne grane	da	Hirurška korekcija u uzrastu 3 god. i 6 mes.	Ne

Slučaj 3 se odnosi na devojčicu koja je rođena sa povećanom porođajnom težinom (TT = 4150 g). Kod ove devojčice sekundarni ASD, kao jedina kongenitalna anomalija, dijagnostikovana je u uzrastu od 21 mesec. Veličina defekta pri dijagnostikovanju bila je 5,5 mm. ASD je bio praćen uvećanjem desne pretkomore; na elektrokardiogramu su bili prisutni znaci atrioventrikularnog bloka I stepena i inkompletnog bloka desne grane. U uzrastu od 34 meseca, veličina defekta se uvećala na 15 mm i bila je praćena znacima opterećenja i uvećanja desne pretkomore i desne komore; dat je predlog za hiruršku korekciju koja je i urađena u 4. godini (3 godine i 6 meseci). Predstavljena Slika 1 odnosi se na EKG nalaz ove devojčice, pre i posle operacije.

Slika 1. EKG trećeg slučaja. A: Pre operacije: normalna osovina; znaci inkompletnog bloka desne grane (2 R zubca - RSR´ u V1; širok S zubac u V6; QRS 0,080 s); negativan T u V1.
B: Posle operacije: normalna osovina; znaci inkompletnog bloka desne grane u V1 odvodu se i dalje prisutni (2 R zubca - RSR´ u V1 i D3 ; QRS 0,082 s); negativan T u V1, bifazan T u V2-V3.

Figure 1. ECG findings in the third case. A: Before surgery: normal axis; signs of the incomplete right bundle branch block (presence of 2 R waves - RSR´ in lead V1; wide S wave in lead V6; QRS 0.080 s); negative T wave in lead V1.
B: After surgery: normal axis; signs of the incomplete right bundle branch block in lead V1 are still present (2 R waves - RSR1; QRS 0,082 s); negative T wave in lead V1, biphasic T in V2-V3.



DISKUSIJA

Od oko 2000 pacijenata čije podatke poseduje autor kao izabrani pedijatar, 15 dece(oko 0,75%) je imalo dijagnostikovan ASD (9 deteta je imalo sekundarni ASD kao izolovanu srčanu manu i 6 deteta je imalo ASD sa pridruženim srčanim anomalijama). Odnos polova dece sa sekundarnim ASD je 6:3 u korist devojčica, podatak koji se podudara sa podacima u svetskoj literaturi [7–10, 17]. Izdvojena su tri slučaja sa različitom dimenzijom defekta u vreme postavljanja dijagnoze, različitim tokom i vremenom zatvaranja. Prema našem iskustvu, na osnovu veličine defekta u vreme dijagnostikovanja, ne može se sa sigurnošću predvideti tok i vreme zatvaranja, kao ni to da li će se defekt spontano zatvoriti ili će biti potrebna hirurška korekcija. Kod devojčice kod koje je defekt bio najveći u vreme dijagnostikovanja (7 mm), najbrže se spontano zatvorio; kod dečaka čiji je defekt bio manjih dimenzija (4,5 mm), bilo je potrebno 6 godina da se defekt spontano zatvori. Treći slučaj imao je nepovoljan tok, zbog čega je hirurška korekcija bila indikovana; naime, dimenzija defekta pri dijagnostikovanju bila je 5,5 mm, a za 13 meseci ona se uvećala na 15 mm i bila je praćena opterećenjem desne pretkomore i desne komore. Azhari i sar. [9] opisali su da se veličina ASD povećavala samo u 6,6% pacijenata. Prema istraživanju Helgason i Jonsdottir [8], u grupi pacijenata sa veličinom ASD 7–8 mm u trenutku dijagnostikovanja, spontano zatvaranje defekta se dešavalo u manjem procentu pacijenata (16,6%). Na neki način, toj grupi pripadao bi opisan prvi slučaj. Procenat spontanog zatvaranja, prema istim autorima, u grupi pacijenata sa veličinom defekta 5–6 mm iznosio je 79%, a manji procenat pacijenata (9,5%) imao je hirurušku korekciju, slično prikazanom trećem slučaju. Upoređujući podatke istih autora i naša iskustva o uzrastu dece u vreme dijagnostikovanja defekta u odnosu na veličinu defekta, navodimo da su ona potpuno drugačija. Naime, prema Helgason i Jonsdottir [8], defekti veličine 4 mm dijagnostikovani su u prvom mesecu, 5–6 mm u trećem mesecu, a 6–7 mm u petom (šestom) mesecu. Kod naše dece, ASD veličine 4,5 mm dijagnostikovan je u drugom mesecu, ASD od 5,5 mm u 21. mesecu, a defekt veličine 7 mm u prvom mesecu života.

Nora i sar. [17] naveli su da je određeni broj pacijenata sa sekundarnim ASD imao i udružene anomalije — ingvinalne i umbilikalne hernije, koje su dijagnostikovane i u naša prva dva slučaja, ili strabizam, koji je dijagnostikovan u našem drugom slučaju. Međutim prikazana dva deteta su bila i prevremeno rođena i sa malom porođajnom težinom (ispod 2000 g), što u dostupnoj literaturi nije bilo navedeno. U istraživanju Nora i sar. [17] takođe postoji podatak da je svega 5% dece bilo prevremeno rođeno, a najmanja telesna težina se kretala između 2000–2500 g. U prethodnom istraživanju nije bilo slučajeva iz blizanačke trudnoće, kao u ovom prikazu.

ZAKLJUČAK

Od oko 2000 pacijenata čije podatke poseduje autor kao izabrani pedijatar, 15 dece(oko 0,75%) je imalo dijagnostikovan ASD (9 pacijenata je imalo sekundarni ASD kao izolovanu srčanu manu a 6 je imalo ASD sa pridruženim srčanim anomalijama). Odnos polova dece sa sekundarnim ASD je 6:3 u korist devojčica.Na osnovu prikazana tri slučaja, možemo zaključiti da se tok zatvaranja ASD ne može sa sigurnošću predvideti na osnovu veličine defekta u trenutku dijagnostikovanja. Potrebno je redovno praćenje dece sa ASD. Pažljiva auskultacija i dalje ostaje važan deo pedijatrijskog pregleda što dokazuju dva slučaja koja su upućena na ultrazvučni pregled nakon utvrdjenog postojanja šuma na srcu u uzrastu 1,5 i 20 meseci. Cilj pedijatra je da svaki slučaj ASD što ranije otkrije kako bi se sprečile moguće komplikacije.

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SEPSIS AND ACUTE KIDNEY INJURY: PATOPHYSIOLOGICAL MECHANISMS AND BASIC PRINCIPLES OF TREATMENT

SEPSA I AKUTNO OŠTEĆENJE BUBREGA: PATOFIZIOLOŠKI MEHANIZMI I OSNOVNI PRINCIPI LEČENJA

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Summary: Sepsis is the main cause of the development of acute kidney injury in critical ill patients in intensive care units. A reinforced and uncontrolled response of the host immune system to bacterial infection has a significant role in the pathogenesis of acute kidney injury in patients with sepsis. Early target therapy, early administration of antibiotics, optimal control of the site of infection, and kidney replacement therapy play a key role in the treatment of patients with sepsis. Continuous dialysis modalities are indicated in hemodynamically unstable patients with severe sepsis, septic shock and acute renal injury. Continuous veno-venous hemodiafiltration with the modified AN69ST membrane provides homeostasis of the immune system's response to bacterial infection, hemodynamic stability of the patient, improved kidney function and a higher survival rate for patients with septic shock and acute renal failure.
Key words: sepsis,acute kidney damage,pathophysiological mechanisms, renal replacement therapy

Sažetak: Sepsa je glavni uzrok razvoja akutnog oštećenja bubrega kod kritičnih bolesnika u jedinicama intenzivne nege. Pojačani i nekontrolisani odgovor imunološkog sistema domaćinana bakterijske infekcije ima značajn uulogu u patogenezi akutnog oštećenja bubrega kod pacijenata sa sepsom. Ključnu ulogu u lečenju bolesnika s sepsomima rana ciljana terapija, rana primena antibiotika, optimalna kontrola mesta infekcije i terapija zamene renalne funkcije. Modaliteti kontinuiranog dijaliznog lečenja su indikovani kod hemodinamski nestabilnih bolesnika s teškom sepsom, septičkim šokom i akutnim oštećenjem bubrega. Kontinuiranaveno-venska hemodijafiltracija sa modifikovanom AN69ST membranom obezbedjuje homeostazu reakcije imunološkog sistema na bakterijske infekcije, hemodinamisku stabilnost bolesnika, poboljšanu funkciju bubrega i veću stopu preživljavanja kod pacijenata sa septičkim šokom i akutnom bubrežnom slabošću.
Ključne riječi: sepsa, akutno oštećenje bubrega, patofiziološki mehanizmi, terapija zamene bubrežne funkcije

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INTRODUCTION

Sepsis is the main cause of the development of acute kidney injury in critical ill patients in intensive care units (sepsis-induced acute kidney injury - SI-AKI) (responsible for 20-50% of cases of acute kidney injury in these patients) [1-2]. The mortality rate of patients with septic shock and acute kidney injury is high and amounts to 50-80% [3]. Epidemiological studies show that 200000 patients die annually in the United States due to sepsis [4]. Critical ill patients in intensive care units with severe sepsis, septic shock and acute kidney failure require prolonged hospitalization, renal replacement therapy (RRT), increased treatment costs and have a high risk of insufficiency of other organs/systems and adverse outcomes. These patients require team approach, enhanced cooperation between anesthesiologists, infectologists and nephrologists. Early detection of sepsis and acute kidney injury, coupled with early target therapy, use of antibiotics and initiation of appropriate supportive therapy can correct the outcome of critical ill patients in intensive care units [5].

Definition of sepsis

Bacteraemia is defined as the presence of bacteria in the blood of patients. The patient's response to a bacterial infection (systemic inflammatory response syndrome -SIRS) is defined as the presence of ≥ 2 of the following criteria: body temperature >38,0^{O}C or <36,0^{O}C, heart rate>90 beats per minute, breathing frequency> 20 respirations in minute or partial pressure of carbon dioxide - pCO_2<32 mmHg, the number of white blood cells>12 x 10^9/L or <4 x 10^9/L or the normal number of white blood cells with>10% immature cell forms. Sepsis is defined as the systemic inflammatory response syndrome to proven infection caused by the bacteria, and severe sepsis as a sepsis associated with organ function disorder - SOFA score ≥ 2 (sequential organ failure assessment - SOFA). Severe sepsis progresses to septic shock, which is defined as a persistent hypotension that does not repair after resuscitation of volume with 0.9% NaCl solution of crystalloid at a dose of 40-60 ml/kg of body mass in the first hour, requiring the use of vasopressor norepinephrine in a dose> 5 μg/kg/min to maintain a mean arterial blood pressure–MAP ≥ 65 mmHg, associated with clinical data for hypoperfusion (serum lactate concentration greater than 2 mmol/l) and organ function disorder (SOFA score ≥ 2). Refractory septic shock is defined as the need for norepinephrine at a dose> 15 μg/kg/min in order to achieve the target value of MAP≥65 mmHg. In intensive care units, for detecting patients with suspected infection or proven infection and adverse outcome, a quick SOFA score (qSOFA) is used. Patients with qSOFA ≥ 2have the risk of prolonged hospital treatment and adverse outcome (altered state of consciousness: the Glasgow Coma Scale - GCS <15, breathing frequency ≥22 respirations per minute, serum lactate concentration greater than 2 mmol/l. In patients with sepsis, with qSOFA score ≥ 2, a standard SOFA score should be made to detect organ function disorders [6]. Renal injury exists if serum creatinine concentration increases by more than 44.2 μmol/l or 0.5 mg/dl compared to basal value, and urine output decreases below 0.5 ml/kg/h. A ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen - PaO_2/FiO_2 ratio <300 indicates a lung function disorder, and GCSless than 15 for brain function disorder [6-7].

Definition of acute kidney injury

For the definition and assessment of the severity of acute kidney injury, clasifications RIFLE 2004(Risk, Injury, Failure, Loss, End-stage), as well as AKIN 2007(Acute Kidney Injury Network) and KDIGO 2012(Kidney Disease Improving Global Outcomes) are used. Based on the AKIN classification, acute kidney injury stage 1 is defined as an increase in serum creatinine by ≥ 26.5 μmol/l (≥0.3 mg/dl) or as an increase in serum creatinine concentration ≥ 1.5times compared to basal creatinine in the serum in the previous 48 hours and/or as a urine output less than 0.5 ml/kg/h for at least 6h. Based on the KDIGO classification, stage 1 of acute kidney injury is present in those patients who have a serum creatinine concentration of 1.5-1.9 times compared to basal, and urine output less than 0.5 ml/kg for 6-12h. The stage 2 of acute kidney injury is characterized by an increase in serum creatinine concentration of 2-2.9 times compared to basal and/or urine output less than 0.5 ml/kg/h for ≥12 h. The third stage of KDIGO classification of acute kidney injuries indicated either by increased serum creatinine

concentration ≥3 times within seven days, or increase in serum creatinine≥354μmol/l (≥4 mg/dl), with an acute increase of 0.5 mg/dL or initiation of RRT, and/or urine output<0.3 ml/kg/h for 24h, or anuria for >12h[8].

INSUFFICIENCY OF ORGANS AND SYSTEMS IN SEPSIS

Acute damage and kidney impairment in sepsis

Pathophysiological mechanisms of the development of acute kidney injury in patients with sepsis may be hemodynamic and non-hemodynamic. Hemodynamic patho-physiological mechanisms include: hypoperfusion of the kidneys, increased intra-abdominal pressure, increased central venous pressure and blood stasis in the venous system of the kidneys. In the last decade, new non-hemodynamic pathophysiological mechanisms of the development of acute kidney injury in patients with sepsis have been discovered: the increased systemic and local responses of the host immune system to infection, increased production and secretion of proinflammatory mediators, "cytokine storm" (disturbance of the balance of proinflammatory and antiinflammatory cytokines in favour of proinflammatory), endothelial dysfunction of the kidney microvasculature, infiltration of renal parenchyma with immune system cells (monocytes / macrophages, neutrophils / leukocytes), activation of epithelial cells of proximal tubules through activation of Toll-like receptors - TLRs and oxidative stress (disorder of equilibrium of oxidative and antioxidative system in favour of oxidative) [9-11].

The enhanced and uncontrolled response of the host immune system to infection plays an important role in the development of acute kidney injury. Microorganisms and their products/molecular structures - pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide, lipoteichoic acid, flagellin, DNA of the bacteria are recognized by toll receptors [receptors that recognize molecular structures - pattern recognizing receptors (PRRs) on the surface of the immune system cells in the peripheral blood (monocytes/leukocytes)]. Activation of these receptors activates the cascade of signals that activate the transcription factors [(nuclear factor kappa B (NFkB), activator protein 1 (AP-1), interferon regulatory factor 3 (IRF3)], all of which results in increased formation and release of proinflammatory cytokines. TLRs are essential for the enhanced activation of the innate immune system of the host to infection caused by bacteria. The immune response of the host can be enhanced by molecules/molecular structures released from necrotic host cells - damage-associated molecular patterns - DAMPs, such as chromatin-associated protein high mobility group box 1 - HMGB1 and heat shockproteins - HSP, histones and oxidatively altered lipoproteins - oxLDL. DAMPs molecules/molecular structures bind to TLR2/TLR4 on the surface of the cells of the innate immune system of the host in the peripheral blood (monocytes/leukocytes) and also stimulate the formation and release of proinflammatory mediators. The recognition of these endogenous molecules/molecular structures results in the development of "sterile inflammation", which contributes to the increased and uncontrolled response of the innate immune system of the host to the bacterial infection (a vicious circle develops). A key role in the development of acute kidney injury in patients with sepsis has the activation of epithelial cells of proximal tubules by PAPMs and DAMPs molecules/molecular structures. PAMPs and DAMPs molecules/molecular structures are filtered into glomeruli, reach to the lumen of proximal tubules, bind to and activate the toll-like receptors (TLR2/TLR4) expressed on the luminal surface of epithelial cells of proximal tubules. Previous studies have shown that the highest significance in the induction of acute kidney damage in patients with sepsis has the pathway of HMGB1-TLR4 signals (response of the local immune system of the kidney). Stimulated epithelial cells of proximal tubules increase the production and secretion of proinflammatory cytokines (the response of the local immune system of the kidney enhances the response of the systemic immune system to the bacterial infection: a vicious circle develops) [9-11].Released proinflammatory cytokines from activated epithelial cells of proximal tubules and infiltrative cells (monocytes/macrophages, leukocytes) induce endothelial dysfunction, disorder of microcirculation of the kidney (peritubular capillary network), ischemia of

epithelial cells of proximal tubules, oxidative stress, mitochondrial function disorder (reduced ATP production) and stop the growth of epithelial cells of proximal tubules in the G1 phase of mitosis. Two key factors involved in the stopping of growth of proximal epithelial cells are insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase 2 (TIMP-2). The results of the research performed so far show that the stopping of growth of epithelial cells of the proximal tubules plays a significant role in the development of acute kidney damage induced by sepsis [12-13]. Detection and clear definition of pathophysiological mechanisms of the development of acute kidney damage in patients with sepsis provides the possibility of developing new strategies for the treatment/protection of epithelial cells of proximal tubules [9-13].

Acute damage and function disorder of the heart in sepsis

Sepsis is an enhanced and uncontrolled response of the immune system of the host to infection, which results in acute damage and disorders of the function of several organs/system of organs, including sepsis-induced cardiomyopathy - SICM. Cardiomyopathy induced by sepsis is defined as an ejection fraction of the left ventricle less than 50% or as a reduction in the ejection fraction ≥10% of the basal ejection fraction and the recovery of myocardial function in two weeks. Pathophysiological mechanisms of acute damage and function disorder of the heart in sepsis can be: hemodynamic (reduced blood flow through coronary arteries, myocardial ischemia, coronary microcirculation disorder and nonhemodynamic (inflammation and infiltration of the myocardial interstitiumby cells of innate immune system), oxidative stress, nitric oxide - NO, endothelial dysfunction, apoptosis and necrosis of cardiomyocytes. In sepsis, microorganisms release PAMPs molecules, such as lipopolysaccharide, lipoteichoic acid, flagellin, and DNA/RNA. These molecules/molecular structures are bound to specific receptors PRRs, such as TLRs on the surface of the cells of innate immune system of the host in the peripheral blood, but also on the surface of the cardiomyocytes. Receptors that recognize molecular structures - PRRs play a key role in enhancing the immune response of the host to the infection. DAMPs, molecules/molecular structures which are released from damaged cardiomyocytes, recognize and bind TLRs on the surface of cardiomyocytes (TLR2/TLR4), stimulate increased formation and release of proinflammatory cytokines (endothelial dysfunction, increased permeability of small blood vessels of myocardial interstitum, infiltration of myocardial interstitium with inflammatory cells, negative inotropic effect of proinflammatory mediators, cardiomyocyte mitochondrial function disorders, oxidative stress, apoptosis and necrosis of cardiomyocytes). All of this results in left ventricular dilatation with normal or low filling pressure, development of systolic heart failure (left ventricularejection fraction - LVEF< 50%) with normal or elevated stroke volume and cardiac index and with possible development of critical reduction in tissue perfusion(septic shock)[14]. Early application of antibiotics and surgical removal of the focus (early control of the site of infection) are crucial for the optimal treatment of patients with sepsis (they reduce the production of PAMPs molecules from bacteria). Optimization of the status of volemia and cardiac function is achieved by the use of crystalloid solution, norepinephrine, and in patients with cardiac index (CI) <2.2 l/min/m^2 administration of levosimendan is indicated (increases the sensitivity of the myofibrils to calcium, improves left ventricular relaxation in the diastolic phase, does not increase the use of oxygen by cardiomyocytes and does not cause heart rhythm disturbances) [14-15].

Acute damage and disorder of function of the liver in sepsis

The incidence of acute damage and disorder of function of the liver in patients with sepsis ranges from 30-50%. In patients with sepsis, two types of liver damage can develop: hypoxic hepatitis (HH), and sepsis induced cholestasis (SIC). HH occurs as a consequence of septic shock due to reduced hepatic perfusion and decreased oxygen utilization by hepatocytes (due to the action of inflammatory mediators and endotoxins) and is characterized by centrilobular necrosis (CLN), a significant transient increase in aminotransferase concentration in the serum in the absence of another possible cause of necrosis of the liver

cells. Clinically, it can also be demonstrated by acute liver failure. Another important pathophysiological mechanism of liver damage in patients with sepsis is cholestasis. The disorder of the bile salts transport occurs as a result of the reduced activity of the bile salt export pump (BSEP), which is located on the canalicular side of the liver cells. The decrease in activity is due to hypoperfusion, hypoxia, and disorder of mitochondrial function of the liver cells: lack of ATP. SIC is clinically manifested as a progressive increase in serum bilirubin concentrations (increase in total bilirubin at the expense of conjugated bilirubin) and jaundice. Due to intrahepatic cholestasis, decreased flow and bile inflow to the lumen of the gastrointestinal tract, there is an atrophy of the mucous membrane of the intestine, loss of bacteriostatic action, increased bacterial translocation and increased serum concentrations of endotoxins in these patients (enhancement of the systemic immune response of the host to bacterial infection) [16-17]. An important role in acute liver damage also has the enhanced response of the systemic and local immune system in the liver of the host to bacterial infection. PAMPS/DAMPs molecules/molecular structures, which bind to specific receptors - PRRs on the surface of the innate immune system cells (monocytes, leukocytes), but also toTLRs (TLR2-TLR6) of the liver and Kupffer cells, have a key role in the enhanced response of the immune system of the host and induction of the gene for the synthesis of proinflammatory cytokines, apoptosis and necrosis of the liver cells (acute liver failure, acutisation of chronic liver failure) [18]. The basic principles of treating acute liver damage in sepsis are early goal-directed therapy - EGDT, volume resuscitation, early antibiotic administration, infection site control, vasopressor support, and restoration of liver perfusion. Medicaments that have the potential to induce cholestasis and hepatocellular damage should be excluded [16-18]. An important role in the treatment of these patients also have thedifferent albumin dialysis modalities [16-18].

Acute damage and disorder of the function of the lung in sepsis

Acute respiratory distress syndrome (ARDS) is defined as an acute condition characterized by severe hypoxia, bilateral pulmonary infiltrates, and absence of evidence of cardiogenic pulmonary edema. An important role in the development of acute damage and lung function disorders (acute respiratory distress syndrome, non-cardiogenic pulmonary edema) has a reinforced and uncontrolled response of the systemic and local immune system to the bacterial infection. PAMPs and DAMPs molecules/molecular structures bind to TLRs on the surface of the innate immune system cells in the peripheral blood (monocytes/leukocytes), as well as on the surface of the epithelial and endothelial cells of the alveolo-capillary membrane of the lungs. After binding to TLRs on the target cells (HMGB1-TLR4), the transcription factor NFkB is activated, and the proinflammatory cytokines are increasingly produced and released. These mediators allow the accumulation of neutrophils and T-cells, apoptosis of epithelial and endothelial lung cells, and the development of non-cardiogenic pulmonary edema. The disease develops 12-48h after the initial event, and is clinically manifested with a feeling of choking and severe hypoxia. The diagnosis of ARDS is based on four criteria: rapid onset, bilateral infiltrates on the chest radiograph, normal cardiac function (pulmonary capillary wedge pressure - PCWP) and PaO_2/FiO_2 ratio less than or equal to 200[19]. These patients are advised to lung protective ventilation strategy - LPVS, with low respiratory volume (tidal volume of 6 ml/kg of ideal body weight), whereby end-inspiratory plateau pressure should be less than 30 cmH_2O using the lowest positive end-expiratory pressure (PEEP = 5-10 cmH2O) by which the satisfactory oxygenation is achieved (PaO_22 = 55-80 mmHg or $SaHbO_2$ = 88 -90%) [20-21]. In severe form of ARDS (severe hypoxemia:PaO2/FiO2<80 mmHg, uncompensated hypercapnia: pH<7.2), the therapy for extracorporeal carbon dioxide removal - ECCO2R is indicated [22].

Acute damage and disorder of the function of the brain in sepsis

Sepsis-associated encephalopathy (SAE) is defined as a diffused brain function disorder that arises as a result of an increased and uncontrolled response of the host immune system to infection in the absence of a direct central nervous system infection. In the development of acute damage and brain function disorders, in patients with sepsis there are

included three pathophysiologic pathways: the neuron/nerve pathway (activation of the afferent nerves, such as vagus and trigeminal nerves), the humoral pathway (cytokines in circulation) and the pathway of altered blood-brain barrier (BBB). All three pathophysiologic pathways activate the microglial cells of the brain (the first detected change in SAE). Activated microglial cells of the brain enhance the production and secretion of nitric oxide, cytokines and free radicals – the reactive oxygen species(ROS), all of which results in the activation of endothelial cells and an increased BBB permeability (vicious circle), disorder of functions of microcirculation of the brain, reduced cholinergic function and altered neurotransmission, mitochondrial function disorder and brain cell apoptosis, development of acute damage and disorder of the function of the brain (encephalopathy associated with sepsis). Precipitating factors include metabolic disorders and use of medicaments. The main clinical features of acute encephalopathy caused by sepsis are: altered state of consciousness, cognitive disorder, cramping attacks and coma. The diagnosis of acute damage and disorder of the function of the brain is based on neurological examination and neurological tests, such as electroencephalography, transcranial Doppler ultrasound, computed tomography and nuclear magnetic resonance. Treatment of SAE consists of the application of early target therapy, early administration of antibiotics, optimal control of the site of infection and precipitating factors (metabolic disorders, use of medicaments) [23].

Acute damage and disorder of coagulation in sepsis

Disseminated intravascular coagulopathy occurs in 35% of patients with severe sepsis (sepsis-induced disseminated intravascular coagulation - SI-DIC). An initial step in the development of DIC in patients with sepsis is the increased accumulation of tissue factor (TF) on the surface of endothelial cells of small blood vessels. As part of the enhanced response of the immune system of the host to bacterial infection, PAMPs molecules/molecular structures of the bacteria (lipopolysaccharide, peptidoglycan) activate TLRs (TLR2/TLR4) on the surface of the immune system cells in the peripheral blood (monocytes, neutrophils). Activated neutrophils enhance the production and secretion of extracellular fibers consisting of DNA and numerous bactericidal proteins such asneutrophil extracellular traps (NETs), which are deposited on the surface of endothelial cells and initiate the process of immunotrombosis. Further, DAMPs such as HMGB1 and histones, release from the activated immune system cells and damaged tissue cells. These molecules activate TLRs on the surface of the endothelial cells, reduce the release of thrombomodulin (TM, anticoagulant effect), increase TF concentration (procoagulant effect), increase the formation and release of proinflammatory cytokines ("sterile inflammation"), stimulate platelet aggregation, lead to blood clots formation in small blood vessels and the development of DIC. TM is an endothelial anticoagulant factor: it stimulates the formation of activated protein C (APC), binds to HMGB1 and promotes its degradation by thrombin,so it prevents/blocks the binding of HMGB1 to the receptor for advanced glycation end products (RAGE) on the surface of endothelial cells. The TM/APC system plays a significant role in maintaining homeostasis of thrombosis and haemostasis, and in maintaining vascular integrity (prevents the development of DIC in patients with severe sepsis) [24-26]. Four clinical forms of DIC syndrome are distinguished: an asymptomatic form, a form with positive results without bleeding and/or thrombosis, a form with increased bleeding and a clinical form with increased thrombosis. The use of recombinant human APC (rhAPC)is associated with a high risk of bleeding. In clinical practice, for the treatment of DIC in patients with severe sepsis, antithrombin III is used (a loading dose of 6,000 IU/30 minutes followed by a continuous i.v. infusion of 6,000 IU/day for 4 days), rhAPC (administered in the form of a continuous i.v. infusion of 24 μg/kg/h for 96h) and recombinant human soluble thrombomodulin (rTM). rTM is applied in patients with SI-DIC accompanied with one or morOorgan dysfunctions, wherein a value of the international normalized ratio (INR) is more than 1.4, at a dose of 0.06 mg/kg/day for six days (i.v. infusion over 30 minutes/day, for six consecutive days) [24-27].

DIAGNOSIS

Indicators of sepsis

The number of leukocytes and serum C-reactive protein concentrations represent the "gold standard" for diagnosing the infection. Procalcitonin (PCT) concentration in serum is used to diagnose sepsis, make a decision for the use of antibiotics, and monitoring of the response to the applied antibiotic. The normal serum PCT concentration is less than 0.05 ng/ml (by some authors less than 0.1 ng/ml). The serum PCT concentration below 0.5 ng/ml indicates local infection and inflammation, with a small risk of progression and severe sepsis (the concentration of PCT should be repeatedly checked over the interval of 6-24h). Sepsis is possible if the serum PCT concentration is 0.5-1.9 ng/ml (grey zone), and serum PCT concentration ≥ 2 ng/ml indicates sepsis. It considers that PCT elevation to 10 ng/ml indicates a severe sepsis, while level higher than 10 ng/ml is associated with the development of septic shock. In patients whose serum PCT concentration is ≥ 2 ng/ml, therapy with antibiotics should be initiated immediately. The use of antibiotics should be discontinued when the concentration of PCT in the serum drops below 0.5 ng/ml [28-29].

Indicators of acute damage and disorder of function of the kidnies

In the last decade, a greater number of new indicators of acute kidney injury have been detected (indicators more sensitive compared to serum creatinine levels): urinary neutrophil gelatinase-associated lipocalin (uNGAL), urinary kidney injury molecule (uKIM-1), a liver-type fatty acid binding protein (L-FABP), urinary IL 18, TIMP-2, IGFBP-7 and cystatin C. The concentration of uNGAL> 150 ng/ml two hours after the initial event indicates the development of AKI. Significant role in the early detection of AKI have the growth factors of proximal tubule epithelial cells: TIMP-2 and IGFBP-7. The combination of TIMP-2 and IGFBP-7 in the urine showed good diagnostic performance in the early detection of the risk of developing acute renal failure within 12 hours. [TIMP-2]x[IGFBP-7] >0.3 (ng/mL)2/1000 was superior for risk assessment of KDIGO stage 2 or 3 AKI when compared to simultaneously measured plasma and urine NGAL, plasma cystatin C, urine IL-18, KIM-1 and L-FABP [30-33].

Indicators of acute damage and disorder of the function of the heart

Cardiac troponins (cTnT/cTnI) are used to detect damage of myocardium caused by ischemia. An increase in troponin levels in serum of ≥ 20% compared to baseline indicates ischemic damage of cardiomyocytes, and values of ≥ 2 ng/ml indicate the development of acute myocardial infarction [34]. For the diagnosis of disorder of cardiac contractile function, natriuretic peptides (BNP, NT-proBNP) are used. In patients with endogenous creatinine clearance greater than 60 ml/min/1.73m_2, heart failure exists if the serum BNP concentration is greater than 100 ng/ml and the concentration of NT-proBNP is greater than 400 pg/ml. If the endogenous creatinine clearance is less than 60 ml/min/1.73m2, the heart failure is indicated by a BNP concentration greater than 200 pg/ml, or NT-proBNP greater than 1200 pg/ml [34].

Indicators of acute damage and disorder of the function of the liver

The most significant indicators of early liver damage are aminotransferases (ALT/AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gammaglutamyl-transpeptidase (GGT), total bilirubin, albumin, and parameters of the blood coagulation system. For hepatocellular dysfunction, serum aminotransferases concentrations are measured, while cholestatic liver damage is defined by an increased concentration of ALP, conjugated bilirubin and GGT [35]. In HH, serum bilirubin concentration is normal or slightly increased, aminotransferase is increased up to 20 times from the upper normal limit, LDH is also increased (LDH > 5000 IU/l), and the ALT/LDH ratio is less than 1.5. Acute damage to the liver induced by medications (hepatocellular damage) indicates an increase in ALT for ≥ 5 and the ratio ALT/ALP ≥ 5. Cholestasis in patients with sepsis shows the total serum bilirubin concentration ≥ 2 mg/dl (≥ 34 μmol/l) (increase of total bilirubin is at the expense of conjugated bilirubin), increased ALP ≥ 2 times in relation to the upper normal limit and ALT/ALP ratio ≤ 2[35, 36].

Indicators of acute damage and disorders of the function of the lung

For early detection of acute lung injury in sepsis, gas analysis (pH, PaO2, PaCO2 and PaO2/FiO2 ratio, sometimes called the Carrico index)are used. For the definition and classification of severity of ARDS by PaO2/FiO2 ratio, the Berlin Classification is used. This definition partitions patients into mild (PaO2/FiO2 200-300), moderate(PaO2/FiO2 100-199), and severe ARDS (PaO2/FiO2<100) and no longer includes the term ''acute lung injury''[37].

Indicators of acute damage and disorder of the function of the brain

For early detection of acute damage and disorder of the function of the brain, a neuron specific enolase - NSE and S100β protein are used [38]. Studies have shown that S100β protein is a better indicator of acute damage and brain function disorders compared to NSE. The normal serum NSE concentration is ≤ 12.5 ng/ml, and the serum protein S100β is less than 0.15 μg/l. On the development of encephalopathy induced by sepsis indicate the NSE values> 24.15 ng/ml and S100β> 0.15 μg/l. Values of S100β ≥ 4 μg/l indicate a severe form of ischemic brain damage [38].

Indicators of acute damage and disorders of the function of the coagulation system

For early detection of DIC in patients with sepsis are used: platelet count, prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), fibrin and fibrinogen-degradation products (FDP), concentration of D-dimer, APC, and serum TM. PT serves to evaluate the external pathway of activation of the coagulation system, and aPTT to assess the activation of the internal pathway of the coagulation system. Thrombocytopenia is an indicator of platelet aggregation induced by fibrin. An important role in homeostasis of thrombosis and hemostasis has a protein C system/activated protein C. The normal concentration of activated protein C in the serum is 1-3 ng/ml. Reduced platelet count (< 100 x 109/l), increased INR (≥ 1.2), prolonged PT (≥ 3s), decreased fibrinogen (< 1 g/l), increased FDP (≥ 10 μg/ml), increased D-dimer (> 1 ng/ml), decreased concentration of activated protein C (APC < 1 ng/ml) and SIRS score ≥ 3 indicate the development of DIC in patients with severe sepsis [39].

PREVENTION AND TREATMENT

Prevention of acute damage and disorders of the function of the kidneys in sepsis

Preventing the development of AKI include EGDT, early administration of antibiotics, and optimal control of the site of infection. Early target therapy involves resuscitation of volume using crystalloid solutions of 0.9% NaCl at a dose of 20-40 ml/kg (2000 ml 0.9% NaCl sol. i.v. inf./60 minutes), during the first three hours of the development of septic shock (along with hemodynamic monitoring). Early target therapy should ensure optimal/adequate hemodynamic stability of patients: central venous pressure (CVP) of 8-12 mmHg, MAP ≥ 65 mmHg, urine output greater than 0.5 ml/kg/h and central venous oxygen saturation (ScvO2) ≥ 70% in the first 6 hours from the development of septic shock. New recommendations indicate that targeted MAP in patients with septic shock should be 80-85 mmHg (especially in patients who had high arterial blood pressure before the development of septic shock). If the target value of MAP is not achieved after resuscitation of volume with crystalloid solutions, norepinephrine (first-line vasopressor) is used, and in patients with CI < 2.2 l/min/m2, inotropic therapy (dobutamine, levosimendan). If hypotension is resistant to norepinephrine, vasopressin is administered at a dose of 0.01-0.03 IU/min. Patients receiving norepinephrine at a dose of 5 μg/min can be added vasopressin at a dose of 0.01-0.03 IU/min. A broad spectrum antibiotic (vancomycin, beta-lactam antibiotics) should be administered within one hour from the development of septic shock, with pre-sampling blood for the hemoculture. A loading dose of vancomycin is 25-30 mg/kg, and it is applied for 7-10 days, and the target vancomycin concentration is 15-20 mg/l. In addition to the use of antibiotics, control of the site of infection is important [40-47]. Early targeted therapy should ensure the restoration of effective arterial volume and perfusion of vital organs [46, 47].

Treatment of acute damage and disorders of function of the kidneys caused by sepsis

Critical ill patients in intensive care units with sepsis (severe sepsis/septic shock) and acute kidney injury require dialysis treatment (according to medical indications). Intermittent hemodialysis is a first-line therapeutic modality in hemodynamically stable patients with acute kidney injury for the treatment of hyperkalemia and life-threatening hypervolemia. Continuous dialysis modalities are indicated in hemodynamically unstable patients with acute kidney injuryassociated with severe sepsis/septic shock, as well as in patients with acute kidney injury associated with acute damage and impairment of the function of other organs (heart, brain, liver, lung). In patients with sepsis and acute kidney injury, the severity of AKI and the presence of absolute criteria for dialysis treatment should be assessed: resistant hyperkalemia (K+> 6.5 mmol/l with or without electrocardiographic changes), resistant hypervolemia (furosemide resistant edema), severe metabolic acidosis (pH of arterial blood ≤ 7.15), complications of high azotemia(uremic encephalopathy, uremic pericarditis) [48, 49].

In the absence of absolute criteria, treatment with dialysis should be started if severe AKIis diagnosed (stage AKIN3/KDIGO3), and in patients with severe sepsis and rapid deterioration of renal function treatment with dialysis should be initiated at stage 2 (AKIN2/KDIGO2) (modulation of response of the systemic and local immune system of the host on infection, clearanceof inflammatory mediators, PAMPs and DAMPs).Prior to making a decision to initiate treatment with dialysis in patients with sepsis and mild/moderate AKI (AKIN 1/2, KDIGO 1/2), treatment objectives should be considered: the severity of the clinical condition of the patient, renal functional reserve, the potential for complications, and clinical conditions that adversely affect the function of the kidneys. The clinical conditions that adversely affect the function of the kidneys are intra-abdominal hypertension and mechanical ventilation with positive ventilation pressure, and agentsthat have toxic effect on kidney tubules are nephrotoxic antibiotics and radiocontrast agents [50-52].

When indication for dialysis treatment is set, it is necessary to choose the appropriate dialysis modality, define the dialysis prescription (dialysis dose, duration, ultrafiltration, bleeding risk, anticoagulation type), patient monitoring, monitoring of extracorporeal circulation (ensuring survival of the hemodialysis filters) and evaluate the dose of dialysis delivered (percentage of delivered/achieved dose of dialysis in relation to the given dialysis dose). Intermittent hemodialysis is used in hemodynamically stable patients with hyperkalemia and hypervolemia that are life-threatening for patients. Intermittent hemodialysis does not affect the clearance of inflammatory mediators (proinflammatory cytokines, antiinflammatory cytokines, PAMPs / DAMPs molecules/molecular structures). The dose of individual treatment of standard intermittent hemodialysis should be aimed to achieve Kt/V index ≥ 1.20 [50-55]. Critically ill patients in intensive care units with severe sepsis/septic shock that are hemodynamically unstable with multiple organ systems failure, increased of serum concentrations ofinflammatory mediators (serum IL-6 ≥ 1000 pg/ml), increased catabolism and hypervolemia require treatment with continuous modalities of dialysis: high-volume veno-venous hemofiltration (HVHF), continuous veno-venous hemodialysis with high cut-offmembranes (CVVHD-HCO), continuous veno-venous hemodiafiltration (CVVHDF) with polymethylmethacrylate (PMMA) and standard / modified acrylonitrile 69 surface-treated (AN69ST) membrane hemofilters [50-56]. HVHFcan be used as continuous with an ultrafiltration rate of 50-70 ml/kg/h (35-80 ml/kg/h) for 24 hours, or as a pulsed high-volume hemofiltration with a rate of ultrafiltration of 85-100 ml/kg/h (100-120 ml/kg/h) for 4-8 hours and then it can be proceeded with a standard dose of 35 ml/kg/h [50-56].HVHF significantly reduces the concentration of inflammatory mediators and restores the balance of the proinflammatory and anti-inflammatory response of the immune system of the host to the bacterial infection [50-56]. CVVHD-HCO appear to achieve greaterclearances of middle molecular weight solutes of 20-50 kDa [inflammatory mediators: IL1b (18 kDa), IL-6 (21 kDa), IL-10 (37 kDa); procalcitonin (13 kDa); myoglobin (17 kDa); β2-microglobulin (12 kDa); Cystatin C (13 kDa); kappa free light chains(25 kDa)] (the pore diameter >0.01 μm, around double than a

standard high-fluxmembrane). In clinical practice, two HCO membranes are used: polyarylethersulfone - septeX® and polysulfone - Enhanced Middle Molecule Clearance - EMiC®. CVVHD-HCO is used in patients with severe sepsis/septic shock and acute kidney damage (AKIN/KDIGO stage≥ 1) at a dose of 35 ml/kg/h for 24 hours (increased risk of albumin loss (65 kDa) and blockers ofanticoagulation: protein C (62 kDa), protein S (69 kDa), antithrombin III (60 kDa) [57-59].

CVVHDFwith PMMA membrane, which has the ability to adsorb the inflammatory mediators (high capacity for cytokine adsorption), is administered at a dose of 35 ml/kg/h, in the course of 24-72h and provides significantly hemodynamic stability and homeostasis of the host's systemic and local immune system responses to infection (prevents the development of "cytokine storm"). When the concentration of IL-6 decreases below 1000 pg/ml, treatment is continued by standard CVVHDF with ultrafiltration of 35 ml/kg/h [60-62]. The standard AN69ST membrane is highly permeable, and binds heparin during the filling the extracorporeal circulation system with heparinized saline solution (during the preparation of the apparatus for the CVVHDF-AN69ST treatment), has a high adsorption capacity for the inflammatory mediators (high adsorption capacity of HMGB1 proteins) and exhibits anti-thrombogenic effects (also referred to as an antithrombotic membrane, SepXiris®). The modified AN69ST membrane is a surface-treated polyacrylonitrile (AN69) hemofilter with a polyethyleneimine (PEI) layer, allowing for incorporation of a heparin layer by priming the membrane in a heparin-saline solution before CVVHDF, thereby significantlyreducing local thrombogenesis when compared with the original AN69 membrane. Also, heparin-primed AN69ST membranes are reportedly more biocompatible with advantages in terms of inflammatory cytokine adsorption.In patients with high risk of haemorrhage, venous anticoagulation is not required, and in patients with normal coagulation status for anticoagulation of extracorporeal circulation, unfractionated heparin is used in a dose of 50% less than the full dose [60-62]. Unfractionated heparin is used for anticoagulation of the extracorporeal circulation as a bolus of 2,000-5,000 IU (30 IU/kg) in the arterial segment of extracorporeal circulation after the blood-pump, and then continues with 5-10 IU/kg/h (target aPTT = 45-55s, 1.5-2 times in relation to the upper normal limit in the blood sample before the filter).In patients with increased risk of haemorrhage (platelet count less than 60 x 109/l, aPTT> 60s, INR> 2), the following options are applied: dialysis without heparin, pre-dilution method of HDF, standard or modified AN69ST dialysis membrane, increased blood flow rate or regional citrate anticoagulation [60-62]. In order to prevent the thrombosis of the filter, it is necessary to monitor the "vital signs" of the extracorporeal circulation: transmembrane pressure - TMP, pressure in the extracorporeal circulation after the blood pump and before the filter - Pin, pressure in the extracorporeal circulation segment after the filter - Pv, pressure gradient - ΔP or "drop" pressure (reduction of pressure that occurs when blood is passing through the filter, calculated as ΔP = Pin - Pv). TMP> 250 mmHg, Pin> 200 mmHg and ΔP> 26 mmHg indicate an increased risk of thrombosis of the filter [63]. For evaluation of the efficiency of AN69ST membrane, serial measurement of urea concentration in effluent and blood of patients - FUN/BUN (measurement at every 12h) is used. The filter is effective if the FUN/BUN ratio is ≥ 0.8, and values less than 0.8 indicate the risk of thrombosis of the filter. For the assessment of the dialysis dose of continuous renal replacement therapy, the ratio of delivered and prescribed dose is calculated (intensity method). CVVHDF is effective if the ratio of delivered and prescribed dialysis is ≥ 80% (the effective treatment time should be ≥ 20h) [64].

Recovery of renal function

The degree of recovery ofrenal function after acute damage affects the long-term outcome of the kidney functions and patient’s condition. One of the goals of treating patients with sepsis and acute kidney injury is to achieve a maximum recovery of renal function.Recovery of renal function in patients with acute kidney injury may occur within the first seven days after initial kidney damage (early recovery). Early recovery of renal function depends on the severity of acute kidney injury, the duration of the acute kidney injury episode, the patient's hemodynamic stability and the functional reserve of the kidneys. Late recovery of renal function can occur in the stage of acute kidney

disease, within a time period of 7-90 days after initial kidney injury[acute kidney disease describes acute or subacute damage and/or loss of kidney function for a duration of between 7 and 90 days after exposure to an acute kidney injury initiating event]. Chronic kidney disease is defined by the persistence of kidney disease for a period of >90 days [65, 66].

Renal function reserve (RFR) describes the capacity of the kidney to increase glomerular filtration rate (GFR) in response to physiological or pathological stimuli. Kidney stress tests are used for the evaluation of RFR (stress tests for the assessment of glomerular and tubular kidney function). In patients with acute kidney injury, a furosemide stress test is used to evaluate RFR. In critical ill patients in intensive care units, with acute kidney injury KDIGO stage 1 or stage 2, furosemide is applied intravenous in a dose of 1-1.5 mg/kg (1.5 mg/kg in patients who had previously received furosemide) and diuresis is monitored for the next two hours. The response to furosemide is appropriate if the urine output is ≥ 200 ml/2h. If an appropriate response is not achieved, this indicates the progression of acute kidney injury, the transition of acute kidney injury from KDIGO2 to KDIGO 3 stage (within 14 days) and the need for dialysis treatment. Stress test with furosemide can also be used to evaluate the end of treatment of AKI with continuous dialysis modalities. After completing the treatment of a continuous dialysis modality, diuresis is monitored during the period of 4h/first-four-period. A good response is defined as the urine output> 400 ml/4h. After thefirst four-hour period, continuous intravenous infusion of furosemide of 0.5 mg/kg/h is included for 4h. After 24 hours from the end of intravenous infusion of furosemide, the diuresis is monitored in a new four-hour period and compared with diuresis from the first four-hour period.Urine output greater than 400 ml/4h and clearance of endogenous creatinine calculated from the volume of urine collected over 4 hours greater than 30 ml/min indicate the absence of need for further dialysis treatment [66-69].

CONCLUSIONS

Sepsis is a common cause of developing acute kidney injury in critical ill patients in intensive care units. A significant role in the development of acute kidney injury in patients with sepsis (severe sepsis/septic shock) has a reinforced and uncontrolled response of the systemic and local immune system to the bacterial infection. ("cytokine storm"). PAMP molecules/molecular structures activate TLRs on the surface of the innate immune system cells (monocytes and neutrophils) in systemic circulation. DAMP molecules activate TLRs on the surface of the epithelial cells of proximal tubules and stimulate the formation of proinflammatory mediators ("sterile inflammation"), which additionally enhances the response of the immune system of the host (vicious circle). Early targeted therapy, early antibiotic administration, and optimal control of the site of infection have a key role in treating patients with sepsis. CVVHDF with AN69ST membrane statistically significantly reduces the concentration of inflammatory mediators as well as PAMP and DAMP molecules in serum of patients with severe sepsis, septic shock and acute kidney injury. It is administered at a dose of 35 ml/kg/h for three consecutive days. When the concentration of IL-6 is reduced below 1000 pg/ml, the treatment should continue with standard CVVHDFin accordance with medical indications. The dialysis is effective if the FUN/BUN ratio is ≥ 0.8 and the ratio of the delivered and prescribed dose of dialysis ≥ 80%. Early sepsis detection, enhanced co-operation of anesthesiologist, infectologist and nephrologist, early target therapy, early antibiotic treatment and early dialysis therapy (continuous veno-venous hemodiafiltration with modified AN69ST membrane) provide a greater degree of recovery of renal function and better outcome for patients with sepsis and acute kidney injury.

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LIST OF ABBREVIATIONS
AKI - Acute Kidney Injury
AKIN - AKI Network
AN69ST - Polyacrylonitrile (surface treated)
AP-1 - Activator Protein 1
APC – Activated Protein C
ARDS - Acute Respiratory Distress Syndrome
BBB – Blood-Brain Barrier
BESP - Bile Salt Export Pump
CI – Cardiac Index
CLN - Centrilobular Cell Necrosis
CVVHDF - Continuous Veno-Venous Hemodiafiltration
CVVHD-HCO - Continuous Veno-Venous High - Cut-Off Hemodialysis
DAMPs - Damage-Associated Molecular Patterns
DIC - Disseminated Intravascular Coagulopathy
LVEF – Left Ventricular Ejection Fraction
ECCO2R - Extracorporeal Carbon Dioxide Removal
EGDT - Early Goal-Directed Therapy
GCS - Glasgow Coma Score
GFR – Glomerular Filtration Rate
HH - Hypoxic Hepatitis
HMGB1 - High-Mobility Group Box 1
HSP - Heat Shock Proteins
HVHF – High-Volume Hemofiltration
IGFBP-7 - Insulin-Like Growth Factor Binding Protein-7
INR – International Normalized Ratio
IRF3 - Interferon-Regular Factor 3
KDIGO - Kidney Disease Improving Global Outcomes
KIM-1 - Kidney Injury Molecule
L-FABP - Liver-type Fatty Acid-Binding Protein
LPVS – Lung Protective Ventilation Strategy
MAP - Mean Arterial Pressure
NETs – Neutrophil Extracellular Traps
NFkB - Nuclear Factor kB
NGAL - Neutrophil Gelatinase-Associated Lipocalin

PAMPs - Pathogen-Associated Molecular Patterns
PaO2/FiO2 - A ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen
PCT - Procalcitonin
PCWP - Pulmonary Capillary Wedge Pressure
PEEP – Positive End-Expiratory Pressure
PMMA - Polymethylmethacrylate
PRRs - Pattern Recognition Receptors
RAGE - Receptor for Advanced Glycation End products
RFR - Renal Function Reserve
RIFLE - Risk, Injury, Failure, Loss, End-stage
ROS – Reactive Oxygen Species
RRT - Renal Replacement Therapy
SAE – Sepsis Associated Encephalopathy
SI-AKI - Sepsis Induced Acute Kidney Injury
SIC - Sepsis Induced Cholestasis
SICM - Sepsis-Induced Cardiomyopathy
SIRS - Systemic Inflammatory Response Syndrome
SOFA - Sequential Organ Failure Assessment
TF – Tissue Factor
TIMP-2 - Tissue Inhibitor of Metalloproteinases-2
TLRs - Toll-Like Receptors
TM - Thrombomodulin

TIMOK MEDICAL GAZETTE

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TWENTY-FIVE YEARS OF ECOLOGICAL TRUTH

DVADESET PET GODINA EKOLOŠKE ISTINE

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Abstract: On the occasion of June 5, the World Environment Day (WED), in 1993, the first ecological symposium "Our Ecological Truth" was organized in Zajecar. The main goal of this meeting is conceived as the possibility to start activities and discussions on ecology and ecological problems in the conditions of war and social crisis, poverty and scarcity of every kind. Soon after its establishment, "Our Ecological Truth" slowly transformed into the ecological movement of the Timocka Krajina. It has become a major driver of environmental activities in the political, scientific, professional and social level. In the last two and a half decades, "Ecological Truth" has evolved and gone through various phases: from a national meeting to an international conference. Ecological Truth has its own mission, which meets every year. Its strength is reflected in its successful living and being held every year in the 21st century. One of the basic tasks of the author of this lecture is an analysis of the achieved results in the period from 1993 to 2017.
Keywords: WED, 1993., conference, ecology, twenty-five years, 2017.

Sažetak: Povodom 5. juna, Svetskog dana zaštite životne sredine, u Zaječaru je 1993. godine organizovan prvi ekološki simpozijum "Naša ekološka istina". Glavni cilj ovog sastanka bio je zamišljen kao mogućnost započinjanja aktivnosti i diskusija o ekologiji i ekološkim problemima u uslovima rata i društvene krize, siromaštva i oskudice svake vrste. Ubrzo nakon osnivanja, "Naša ekološka istina" se polako transformisala u ekološki pokret Timočke Krajine. On je postao glavni pokretač aktivnosti na zaštiti životne sredine na političkom, naučnom, stručnom i društvenom nivou. Za poslednje dve i po decenije, "Ekološka istina" je evoluirala i prošla kroz razne faze: od nacionalnog skupa do međunarodne konferencije. Ekološka istina ima svoju misiju, koja se ispunjava svake godine. Njena snaga se ogleda u njenom uspešnom postojanju i u tome da se održava svake godine u 21. veku. Jedan od osnovnih zadataka autora ovog predavanja je analiza postignutih rezultata u periodu od 1993. do 2017. godine.
Ključne reči: 1993., konferencija, ekologija, dvadeset pet godina, 2017.

INTRODUCTION

Preparing for this lecture, the authors were considering whether the twenty-five years of the continuous duration of the "Ecological Truth" was a long enough period to look back and find out which one of the benefits of such a scientific conference of international reputation was used, and how far the development of ecological idea has gone and which way it should go further. Furthermore, is something like that so necessary at all today, when the "Ecological Truth" continues its way on, as it was before? For the first time, such a look back was made after ten such conferences [1]. It was quite a lot of work that needed to be done: regarding the definition of ecology and harmonization of ecological terms and concepts, expert-methodological and essential approach to ecology as a science and the possibilities of its use in everyday life. Ecology is a young science, with an interesting history. The term "ecology" was first used by Ernst Hekel, a follower of the great Darwin, defining it through the relations with the surrounding environment including, in the broadest sense of the word, all the existential relationships of living beings and the environment [2]. Ecology is the science of life, which provides the scientific basis for the protection of nature. The term human ecology is also used, most often when it comes to ecological analyses and activities that go hand in hand with the leading political elites and modern economies and their institutions, in order to

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maintain production that is harmful to the environment and when it wants to maintain an environmentally harmful order - homo tehnicusa [3].
The definition of ecology and functioning of the ecosystem is also found in the "Framework of Life" [4] of our scientist Sinisa Stankovic, born in Zajecar.

WHAT PRECEDED ECOLOGICAL TRUTH?

Hygiene - medical ecology

In the sixties of the last century, at the time when the development of industrialization took place, it was necessary, within the framework of the program of "reconstruction and development of socialism" in Yugoslavia, to build factories, restore mines, build electric power plants, railways and roads in the Timok region, to restore the economy as a whole, and to increase the production especially in Bor and Majdanpek. We will also mention here the impacts on the nature, life and health of the population that were created by the construction of the HPP "Djerdap I", where the interventions on the Danube and the riverbank were such that they significantly influenced the flora, fauna and population both on our and Romania's side. At that time, the ecological fate of this area was altered.

At that time, the Institute of Hygiene in Zajecar was founded with a purpose to monitor the impact of the environment on human health, at first, in industrial plants, and later to spread out, to control the impact of air, noise, lighting and temperature in the manufacturing plants on the health of workers, and later the quality of toxic gases and wastewater from industrial plants and other harmful effects on the environment. Doctors were sent to specialize in hygiene, a medical science with attributes of medical ecology. The institute was equipped with adequate equipment, it employed technicians, chemists and toxicologists and gave the first results regarding the state of the environment in the Timok Krajina region.

Bor mine - the biggest polluter of the environment in Yugoslavia

The results of laboratory investigations of the quality of air, watercourses and soil clearly show that in the seventies, Bor and its surroundings were the most polluted and most devastated areas in Yugoslavia. The Timok river became a collector of industrial waters of the Bor copper mine, in which every form of life ceased to exist. It should be said that the Timok river was at the same time a collector of wastewaters from the industry and cities of Knjazevac, Zajecar and Boljevac. During the spring floods, the Timok was poisoned by poisonous pyrites and it permanently destroyed fertile soil from the Vrazogrnac river to its confluence in the Danube from year to year. The peasants from Brusnik, Bracevac, Tamnica, Rajac, Rogljevo and Kovilovo were left without more than a thousand hectares of fertile land. The peasants from the Bulgarian villages, downstream of Bregovo, suffered damage too.

As far as the Bor mine is concerned, in all the reports and analyses, which always had the significance of a political message, there were always just praises. No harmful impacts on the environment, nor a proposal for measures to stop further degradation of nature and sanitize the consequences. A similar situation was in Majdanpek. The Country needed copper and gold. The political and economic elites in Yugoslavia were satisfied.

Ecological incidents, rebellions and meetings

The peasants, who were partly miners in nearby mines and factories in the cities nearby, weren't satisfied with the progress of industry and mining in the Timok region. After World War I, the development of mining in this region caused the degradation of the land and the great dissatisfaction of the population due to such destruction of nature and fertile soil. It was the reason for the peasants' rebellions in the surrounding of Bor, below Rtanj and in the vicinity of Vine. Thus, the "Bulletin of the Moravian Banovina Chamber of Commerce" published in the number 3, January 1, 1939, the following article: "The coal mine Rtanj discharges its coal mine black water in the Mirovstica River, and further into the Black River. From polluted water, the fish died and the animals were killed, especially during drought. Taking this into account, our chamber has threatened the Ministry of Forests, Mines and Banks, asking to protect the interests of agriculture in this region [5]".

Much worse situation was in the vicinity of Bor and along the Borska river and in the vicinity of other mining and industrial plants between the two wars. On May 7, 1935, the following was written about the rebellion of peasants from the Bor region in the Letopis of Bor Parrohi and the Church: „On that day,

peasants from Bor, Slatina, Krivelj, Ostrelj, Brestovac, Bucje, Metovnica and Bela Reka, with skillful concentration and sudden attack, stopped the operation of the copper smelter in the Bor mine after they had beaten some of the personnel in the smelter and banned the work. They were desperate and forced to do it because of the destructive effect of poisonous smoke from the smelter on their crops, soil and cattle. From that day till the 31st of May the smelter did not work, so there was the grace to watch the plants develop and the fields covered by greenery. In the absence of toxic smoke from the smelter, farmers' crops began to progress and even some birds that had not existed before appeared, and with their tweetment, gave life and joy to nature. But on June 1, the Smelter started working again and the smoke from it began to cover, with the fading death, trees, grass, fields, and even the birds under its influence were expelled. - Ah! When will the poisonous effect of this smoke finaly disappear ? When the righteous desire of the peasant will be fulfilled, that the smoke does not destroy the soil, his cattle and his health! [6]".

After the demolition of a dam on the lake where waste waters and pyrite from the mine in Majdanpek were collected, the village of Debeli Lug and the riverbank area were flooded to the mouth of the river Pek into the Danube. Residential buildings, stables and yards in Debeli Lug were flooded with toxic wastewater and pyrite, arable land was endangered and living organisms were destroyed in the water of the Pek River and the Danube.

In the mid-seventies of the 20th century, the communal environment of Zajecar was burdened with industrial pollution from a glass factory, from steam locomotives at the railway station and individual fireplaces. The public was especially harassed by the pollution from industrial plants in the glass factory. In those years, the measurement of air pollution in the communal environment started. After three years of measurement, it was shown that the air was polluted by the contents of the vapor from the glass factory, and it was ordered that measures be taken to reduce the pollution. There were suggestions that the railway station should be moved to another location, thus reducing air pollution by smoke from steam locomotives. This did not happen because these were soon replaced by electric motor trains. In Bor, the situation was even worse, because the level of pollution in the municipal environment of industrial gases was above the maximum concentration allowed daily.

The situation did not improve much, so the population's dissatisfaction led to an ecological meeting in the center of Zajecar in the early 1990s, attended by about 3,000 people. A few days later an ecological meeting was organized in Bor, too [7].

Figure 1 Ecological meetings in Zajecar and Bor
Slika 1 Ekološki skupovi u Zaječaru i Boru

Such a public opinion process was inspired by the increased involvement of professional institutions from Zajecar and Bor, in solving the ecological crisis in the Timok Krajina region and establishing an environmental tribune "Ecological Truth".

The Stockholm Conference in 1972 and her echo in Timok Krajina

The first United Nations Conference on the Human Environment was held in Stockholm in 1972. This Stockholm Conference marked a

milestone in the relationship between humanity and the environment. The first day of the Conference in Stockholm, June 5, was proclaimed World Environment Day (WED). From this Conference, a malicious, apocalyptic message spreads, that if the pollution and destruction of nature, continues at the same pace, life on earth will disappear in the next 50 years! Warning alarm was on as a reminder that natural resources can not be exploited uncontrollably and excessively without consequences for the overall humanity. In the focus of interest, the "polluters", protected by politics, were found in the focus of interest in the whole of the Timok River basin, and over the hill, in Majdanpek. Cadastres of polluters were being made rapidly. At first, the state was satisfied that "polluters" were paying expensive ecological taxes, because of the damage they inflict on nature. Problems to be solved are very complex and expensive for interventions to be taken on obsolete technologies and to make their harmful effect to nature more tolerable. The problems caused by the development of all cities and the urbanization of the Timok Krajina region should be also added to all this. There was a need to deal with the problems created by intensive industrialization of the Timok region by developing institutions and strategies based on science in the field of nature protection from industry and obsolete technologies.

Echo of the Conference in Rio in 1992 - new approaches to ecology

The Rio de Janeiro Conference, twenty years after the Stockholm conference, focused on preserving natural values, especially on biodiversity. While the first was concerned with environmental issues, the second tackled environmental and developmental issues and was known as the World Earth Summit. The global concept of sustainable development was officially accepted and adopted at this conference [8].

The Institute for Health Protection "Timok" in Zajecar has introduced a new philosophy in the ecology of the Timok Krajina region, which also reflects on the contents of the work of "Ecological Truth". At the time when this was not taken into account in Serbia, and when many did not know what biodiversity is, the Institute initiated and organized the scientific conference "Our Ecological Truth", thus drawing attention to new approaches to ecology.

The following attitude is taken into account: it is better to protect natural biodiversity more effectively than to wage war with "polluters". So the issue of ecological education came to the agenda. The results of the research unambiguously indicated low ecological awareness among the population and insufficiently developed health culture.

The Institute offered a school system the Ecological education program, which began to be applied in some secondary schools in Bor and Zajecar. Elementary school in the village of Krivelj had organized for several years "School of ecology" in the village of Gornjane, to which came elementary school pupils from several cities from Serbia and Vojvodina. The papers about ecological education referenced in a series of scientific conferences of "Ecological Truth" is a proof of the echo the Conference in Rio had in our area.

Community for Science and "Ecological Truth"

Nikola Sainovic started the founding of the Society for Science in Bor in 1986. The first scientific project for the protection of the human environment was related to the so-called. «Floodplain», created after the construction of the hydroelectric power plant " Djerdap I".

Figure 2 Participants of the "School of ecology" in the village of Gornjane
Slika 2 Učesnici "Škole ekologije" u selu Gornjane

It was hosted by several institutions and researchers, led by Academician Vojislav Petrovic, professor of biology, born in Krajina, a former professor of Negotin Gymnasium. Several doctors from the area of the Timok region, who wanted a taste of the eternal grail of science, were also included in a large team of experts of the project. A microbiologist, a toxicologist and a doctor of preventive medicine were engaged in the Institute for Health Protection "Timok" Zajecar, together with the Institute for Copper in Bor and the Technical Faculty in Bor and the Institute seriously began to deal with ecology. We had laws, a scientific community, institutions, but there was something else missing: an environmental forum where research results, environmental ideas, research approaches, discussions, research and interventions in a damaged nature could be presented. And most importantly, to offer efficient expert solutions to factories and the state and to facilitate the implementation of environmental laws.

What was at first interesting was the fact that researchers began to pay attention to the risks and health-related hazards caused by industry and technology. And not only that.The presence and engagement of the Institute in Zajecar has contributed to the protection of nature with special values: moral, institutional and scientific.

During participation in the work of the Community of Science, Rade Kojdic - Cica, Director of the Institute of Copper Bor, Director of the Zavod for Health Protection "Timok" Zajecar, Dr Petar Paunovic, and Toplica Marjanovic from Bor, launched an initiative for holding an annual professional and scientific conference "Our Ecological Truth", later "Ecological Truth", today "Ecological Truth and Environmental Research".

The first Conference entitled "Our Ecological Truth", was held on June 5, 1993 in Zajecar. The representatives of the Ministry of Environmental Protection, local governments, businesses, NGOs, the media and doctors of medical centers of the cities in the region of Timok Krajina took part in the conference. The papers from this scientific conference were published in the Journal "Razvitak" in Zajecar.

Figure 3 Journal "Razvitak" from 1993
Slika 3 Časopis "Razvitak" iz 1993. godine

Our Ecological Truth and Radioactive Waste from Vinca

Soon after its establishment "Our Ecological Truth", slowly began to transform itself into ecological movement of Timok Krajina region. It has become a serious institution of ecological activities on political, professional and social plan. In the middle of the 90s, during a scientific and expert meeting held on Borsko Lake, Dr Jordan Aleksic, minister of Ecology and Environmental Protection of the Republic of Serbia, raised a question regarding the radioactive waste from Vinca, having a doubt that the waste had been deposited in the abandoned uranium mine in Kalna [9].

Kladovo Community has raised the issue of pollution of the Danube by radionuclides from the waste waters coming from those European countries through which this big river flows. The community was also looking for a solution on how to protect vegetable fields from the destruction caused by acid rains formed due to air polluted by industrial emissions from the factories in Turn Severin, in neighboring Romania. This opened up a space for researchers and topics that found their place in the programmes of scientific – expert meetings of Ecological Truth.

LEAP - Local Environmental Action Plan

Numerous and varied activities in the field of environmental protection enabled the LEAP - local environmental action plan to be created at the beginning of a new period in 2000, in order to ensure the continuity of human environment protection. The largest number of municipalities in the Timok Krajina region have developed ecological plans upon state's directives, but these have not been revised, due to political and economic crisis. "Ecological truth" continued to live in spite of the war and the mentioned crisis.

TWENTY-FIVE YEARS OF ECOLOGICAL TRUTH

"Ecological Truth" is a traditional scientific and professional conference, today a conference devoted to environment, ecology, public health, sustainable development, and its primary goal is to raise ecological awareness. It has been held for 25 years and, most importantly, it fulfills this mission.

"Ecological Truth" began in 1993 as a national conference, later a national scientific with international participation, and today it is an international conference. In the past two decades, "Ecological Truth" has developed and gone through certain phases of its development. However, the years 1994, 1996, 1998, 1999, 2003 and 2010 represent the milestones in the development of the "Ecological Truth".

In the spring of 1994, the Institute offered cooperation to the Society of Young Researchers and to the Mining and Smelting Combine Bor to jointly continue with the organization of this event. This was one of the crucial moments when the foundations of future organization and cooperation were laid. On this occasion, some strategic decisions were made:

1. "Our Ecological Truth" was to become a multidisciplinary scientific-expert conference on natural values and environmental protection, where the latest scientific, theoretical, expert knowledge and practical experience of experts of different profiles (engineers, doctors, biologists, geographers, free planners , economists, lawyers, pedagogues) would be heard.
2. At the same time, the "Days of Preventive Medicine of Timok Krajina", which, by then, had already been organized for five years, was to be organized together with the "Ecological Truth".
3. Apart from the Institute, some other professional and scientific, health and economic organizations as well as non-governmental organizations from Bor and Zajecar would be included in the organization of the Conference.
4. The Conference should become traditional and be organized in all the cities of Timok Krajina.

According to the number of papers, authors and co-authors, as well as the participants, the second "(Our) Ecological Truth" was the most massive event to date. A Proceeding of abstract papers was prepared for the Conference (up to 2 pages per work).

Each new conference brought up some new dilemmas and sought answers to new questions. Preparations for the third conference began with the question: Should such a Conference be organized each year? Do we have enough knowledge, readiness, organizational and financial capabilities? The solution was found in the establishment of cooperation between professional and scientific institutions, economy, local self-government and non-governmental sector, which ensured successful organization.

The following co-organization of the conference in 1995, included the only state higher education institution in the Timok Krajina region, the Technical faculty in Bor. The Technical faculty in Bor had actively participated in co-organizing of the event until 2002, and since 2003, until today, it has been the main organizer of the "Ecological Truth". During this period, the Technical faculty in Bor has made a considerable contribution to the realization of the idea begun in 1993.

In 1996, this scientific conference was named "Ecological Truth" at the proposal of Assist. Prof. Dr. Goran Belojevic from the Institute of Hygiene and Medical Ecology at University of Belgrade, who was one of his regular participants.

In 1998, it brought in some new things, which enriched the content and program of this event and brought it closer to the wider public. From the beginning, one of the basic goals of the Conference was the affirmation of the research work of young people. At the sixth meeting, in 1998, for the first time they had the opportunity to present their papers to pupils and students within the special section " Scientific youth", and this idea was also accepted at other scientific meetings in Serbia.

The "Ecological Truth" was the only traditional scientific conference organized in wartime in 1999. It was held in Zajecar on the last day of the NATO bombing and on the first day of peace.

Due to a large interest shown by many experts from the country and abroad, this conference further developed and on its 18th birthday in 2010, for the first time it was held as international conference and out of eastern Serbia. The venue was in Banja Junakovic near Apatin, in Vojvodina. Accepted papers are printed in English in Proceedings. The title of the conference was the International Conference "Ecological Truth", officially used by 2017. The late Prof. Dr. Zoran S. Markovic then stated: „This is one of the multidisciplinary, international conferences in Serbia that has the official approval of the Ministry of Education, Science and Technological Development.“

In 2010, of the previous co-organizers, there only remained the Society of Young Researchers from Bor; new co-organizers were: Zapadno Bacка Administrative District Sombor, Public Health Institute of Sombor, Vojvodina Forest of Sombor, Chamber of Commerce Novi Sad, DP „Agroinstitut“ Sombor, Municipality of Apatin and Sombor City.

Figure 4 Participants of the "Ecological Truth" in Zajecar, 1999.
Slika 4 Učesnici "Ekološke istine" u Zaječaru, 1999. godina

Bearing in mind that in the realization and affirmation of "Ecological Truth", various government, professional and scientific and numerous non-governmental organizations have participated from the very beginning, it is necessary to get to know the nature and basic characteristics of "Ecological Truth".

The basic characteristics of the Conference "Ecological Truth" are:

- Science and expertise: the main goal is the presentation of scientific and professional papers reviewed by the Scientific Committee. All papers were published in special Proceedings, which affirmed the participants and their ecological activities.
- Multidisciplinarity and interdisciplinarity: the organizer's desire was to gather experts from different profiles at the same place and to share knowledge about the environment and people's health from

the aspect of different sciences, and also to point out possible solutions to the same topic.

- Relevancy and adaptability to the needs of the time: the number of different topics and sections in which they are dealt with can always be searched for current scientific developments and practical needs of the society. Some sections expanded their scope of work and introduced new sections with contemporary content, for example, since 2001, there has been a session on the Local Environmental Action Plans (LEAP), which became a special topic at the moment when we began to talk about these plans.
- Affirmation of research work of young people: since the first scientific conference special attention has been paid to the affirmation of the research work of young people.
- Co-operation and capacity building of the local community: the organization of such an event required the establishment of cooperation of the entire community. One of the goals was to achieve cooperation and strengthen the capacities of all sectors: government (local self-government), business sector, professional and scientific institutions and non-governmental organizations.
- Publicity: the conference is seen as an opportunity to inform the public about new scientific knowledge about the environment. Therefore, from the beginning, all the information has been available to the media and every opportunity was used to talk and write about it.

An analysis of the results achieved at the professional and scientific conference "Ecological truth" is one of the basic tasks of the author of this lecture. Tables 1 to 8 provide statistical analysis of results and events in the period from 1993 to 2017.

The number of published papers at the conference "Ecological Truth" from 1993 to 2017 is presented in tables 1 – 3.

Table 1 Number of published papers on the national scientific and professional conference "Our Ecological Truth" (1993-2002)
Tabela 1 Broj objavljenih radova nacionalne naučno-stručne konferencije "Naša Ekološka istina" (1993-2002)

SEKCIJA	OUR ECOLOGICAL TRUTH										
	Ordinal numbers of Conferences										
	I	II	III	IV	V	VI	VII	VIII	IX	X	∑
EI1. Plenary lectures	10	-	-	-	-	-	-	-	-	-	10
EI2. Technology and the state of environment	-	61	55	45	44	26	5	20	22	20	298
EI3. Protection and preservation of natural resources	-	33	18	12	20	18	13	21	18	13	165
EI4. Ecological education	-	11	11	8	21	6	11	20	10	13	111
EI5. Water accumulation – state, problems and perspectives	-	5	7	-	-	-	-	-	-	-	12
EI6. Use and water protection	-	-	-	-	-	9	8	8	11	12	48
EI7. Food and nutrition of the people	-	13	13	-	-	-	-	-	-	-	26
EI8. Nutrition and health								12	10	10	32
EI9. Agriculture	-	-	-	-	-	-	10	10	10	8	38
EI10. Economy and environmental protection, standardization and homologization of standards	-		6	5	-	-	-	-	-	-	11
EI11. Ecological management	-	-	-	-	-	7	2	14	13		36
EI12. Urban ecology	-	-	-	-	-	-	5	11	9	20	45
EI13. Sustainable tourism	-	-	-	-	-	-	-	-	-	5	5
TOTAL EI	10	123	110	70	85	66	54	116	103	101	838
SESSION	DAYS OF PREVENTIVE MEDICINE OF TIMOK KRAJINA										
	Ordinal numbers of Conferences										
	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	∑
PM1. Environment and heath	-	12	18	-	-	4	-	-	-	-	34

PM2. Energy and health	-	-	-	-	-	-	-	-	4	-	4
PM3. Migration and health	-	-	-	2	1	-	-	-	-	-	3
PM4. Demographic processes in SRJ	-	-	-	-	-	4	1	6	9	18	38
PM5. Preventive medicine	-	-	8	-	-	-	-	-	-	-	8
PM6. Preventive medicine in health protection today	-	-	6	-	-	-	-	-	-	-	6
PM7. Health of people during the last decade of the XX century	-	-	-	19	-	-	-	-	-	-	19
PM8. Prevention and suppression of chronic mass disorders of health – modern achievements	-	-	-	-	-	-	7	11	8	3	29
PM9. Social- ecological health model in theory and practice	-	-	-	-	12	7	-	-	-	16	35
PM10. Health education and social medicine	-	15	-	-	-	-	-	-	-	-	15
PM11. Hygiene	-	30	-	-	-	-	-	-	-	-	30
PM12. Epidemiology and microbiology	-	28	-	-	-	-	-	-	-	-	28
PM13. Modern ecological-epidemiological approachin solving natural focal infections	-	-	-	3	2	-	-	-	-	-	5
PM14. Quality control of immunization	-	-	4	1	-	-	-	-	-	-	5
PM15. Lyme, 20 years later	-	11	-	-	-	-	-	-	-	-	11
PM16. Microbes and people	-	-	-	9	7	11	6	15	14	7	69
TOTAL PM	0	96	36	34	22	26	14	32	35	44	339
	SPECIAL SESSIONS										
PS1. Scientific and research projects	-	-	-	-	-	4	-	1	1	2	8
PS2. National and local ecological action plans	-	-	-	-	-	-	-	-	2	6	8
PS3. Scientific youth	-	-	-	-	-	12	-	19	26	31	88
TOTAL PS	0	0	0	0	0	16	0	20	29	39	104
TOTAL PAPERS (EI+PM+PS)	10	219	146	104	107	108	68	168	167	184	1281

Table 2 Number of published papers on the scientific and professional conference on natural resources and environmental protection "Ecological Truth" (2003-2009)
Tabela 2 Broj objavljenih radova nacionalne naučno-stručne konferencije na temu prirodnih resursa i zaštite životne sredine "Ekološka istina" (2003-2009)

SESSION	SCIENTIFIC AND PROFESSIONAL CONFERENCE ON NATURAL RESOURCES AND ENVIRONMENTAL PROTECTION "ECOLOGICAL TRUTH"							
	Ordinal numbers of Conferences							
	XI	XII	XIII	XIV	XV	XVI	XVII	∑
EI1. Plenary lectures	4	2	1	1	1	1	5	15
EI2. Protection and preservation of natural resources	23	16	14	14	14	17	18	116
EI3. Technologies, wastes recycling and the environment	22	22	31	28	18	31	-	152
EI4. Technological aspects – natural values and their protection	-	-	-	-	-	-	20	20
EI5. Nutrition and health	5	5	13	3	5	6	10	47
EI6. Agriculture	3	14	11	13	14	12	-	67
EI7. Urban ecology	20	15	13	11	14	8	-	81
EI8. Air protection	-	-	-	-	-	-	13	13
EI9. Water supply and protection	10	10	19	9	7	7	7	69
EI10. Land protection	-	-	-	-	-	-	6	6
EI11. Energy efficiency	-	-	-	-	-	3	-	3
EI12. Waste management and secundary materials recycling	-	-	-	-	12	12	-	24
EI13. Ecological management	5	7	8	9	9	5	-	43
EI14. Ecological ethics, ecological education, NGO and the environment	8	9	10	6	13	5	-	51

EI15. Municipality and environmental protection	-	-	-	-	-	2	26	28
EI16. Sustainable development	-	-	-	-	12	7	-	19
EI17. Sustainable tourism	5	4	6	16	-	-	-	31
EI18. Round table	-	-	-	3	3	3	-	9
TOTAL EI	105	104	126	113	122	119	105	794
SESSION	DAYS OF PREVENTIVE MEDICINE OF TIMOK KRAJINA							
	Ordinal numbers of Conferences							
	16.	17.	18.	19.	20.	21.	22.	∑
PM1. Socio-ecological health model in theory and practice	6	2	12	-	6	12	-	93
PM2. Prevention and eradication of massive health disorders - the latest developments	3	15		-	5		-	
PM3. Microbes and people (interweaving of macro and micro environment in all spheres of life	5	-	-	-	-		-	
PM4. Demographic processes	14	4	9	-	-		-	
TOTAL PM	28	21	21	0	11	12	0	93
	SPECIAL SESSIONS							
PS1. Scientific and research projects	-	3	3	2	-	-	-	16
PS2. National and local ecological action plans	6	2			-	-	-	
PS3. Scientific youth	16	23	-		4	5	12	60
TOTAL PS	22	28	3	2	4	5	12	76
TOTAL PAPERS (EI+PM+PS)	155	153	150	115	137	136	117	963

Tabela 3 Number of published papers on the International scientific – professional conference "Ecological Truth"(2010-2017)

Tabela 3 Broj objavljenih radova o međunarodnoj naučno-stručnoj konferenciji "Ekološka istina"(2010-2017)

SESSION	INTERNATIONAL SCIENTIFIC AND PROFESSIONAL CONFERENCE "ECOLOGICAL TRUTH"								
	Ordinal numbers of Conferences								
	XVIII	XIX	XX	XXI	XXII	XXIII	XXIV	XXV	∑
EI1. Plenary lectures	-	2	2	1	1	4	4	5	19
EI2. Protection and preservation of natural resources	10	10	18	10	7	8	7	5	75
EI3. Technologies, wastes recycling and the environment	26	26	24	29	30	47	40	31	253
EI4. Energy efficiency, environment and climate	6	6	1	5	7	7	8	-	40
EI5. Soil and water conservation engineering	10	-	10	13	4	-	19	8	64
EI6. Agriculture: agribusiness, agro-engineering and organic food production	5	5	2	-	5	7	8	-	32
EI7. Nutrition and health	4	-	1	4	-	-	5	8	22
EI8. Urban ecology	5	12	15	6	5	13	-	-	56
EI9. Water supply and protection	3	9	-	-	6	4	-	6	28
EI10. Ecological management (Law, economy, standardization)	3	6	5	13	13	6	17	7	70
EI11. Ecological ethics and ecological education	3	7	3	4	4	6	14	-	41
EI12. Environmental ampact assessment	4	1	1	9	5	-	-	19	39
EI13. Eco tourism and sustainable development	3	4	4	3	3	7	-	7	31
EI14. Preventive medicine and ecology	5	14	4	7	6	7	6	-	49
TOTAL EI	87	102	90	104	96	116	128	96	819
		SPECIAL SESSIONS							

PS1. Students' papers	1	6	9	4	-	-	-	-	20
TOTAL PS	1	6	9	4	0	0	0	0	20
TOTAL PAPERS (EI+PS)	88	108	99	108	96	116	128	96	839

The organizers and co-organizers of the conference "Ecological Truth" from 1993 to 2017 are presented in tables 4 – 6. The venue and the Presidents of the Scientific and Organizing committee of the conference "Ecological Truth" from 1993 to 2017 are presented in table 7. The number of authors and publications of papers at the conference "Ecological Truth" from 1993 to 2017 are presented in table 8, too.

Table 4 Organizers and co-organizers of the national scientific and professional meetings "Our Ecological Truth" (1993-2002)
Tabela 4 Organizatori i suorganizatori nacionalnih naučno-stručnih skupova "Naša Ekološka istina" (1993-2002)

ORGANIZER	OUR ECOLOGICAL TRUTH									
	I	II	III	IV	V	VI	VII	VIII	IX	X
University of Belgrade, Technical Faculty in Bor			X	X	X	X	X	X	X	X
Institute for Public Health "Timok" Zajecar	X	X	X	X	X	X	X	X	X	X
Society of Young Researchers Bor		X	X	X	X	X	X	X	X	X
Institute for copper Bor		X						X		
RTB BOR Group		X	X							
Health Center Bor		X	X							
Ministry of Environment and Development SRJ		X								
Ministry of Environmental Protection RS		X								
Community of Negotin						X				
Center for Agricultural Research Zajecar						X	X	X	X	X
Ecological movement "Dubasnica"						X				

Table 5 Organizers and co-organizers of the scientific and professional conference on natural resources and environmental protection "Ecological Truth" (2003-2009)
Tabela 5 Organizatori i suorganizatori naučno-stručne konferencije na temu prirodnih resursa i zaštite životne sredine "Ekološka istina" (2003-2009)

ORGANIZER	SCIENTIFIC AND PROFESSIONAL CONFERENCE ON NATURAL RESOURCES AND ENVIRONMENTAL PROTECTION "ECOLOGICAL TRUTH"						
	XI	XII	XIII	XIV	XV	XVI	XVII
	EkoIst'03	EkoIst'04	EkoIst'05	EkoIst'06	EkoIst'07	EkoIst'08	EkoIst'09
University of Belgrade, Technical Faculty in Bor	X	X	X	X	X	X	X
Institute for Public Health - Zajecar	X	X	X	X	X	X	X
Society of Young Researchers Bor	X	X	X	X	X	X	X
Institute of Mining and Metallurgy - Bor							
Center for Agricultural Research Zajecar	X	X	X	X	X	X	
RTB BOR Group							
Health Center Bor							
Ministry of Environment and Development SRJ							
Ministry of Environmental Protection RS							
Community of Negotin							
Ecological movement "Dubasnica"							
University of Nis, Faculty of Occupational Safety Nis					X	X	

Table 6 Organizers and co-organizers of the International scientific – professional conference "Ecological Truth" (2010-2017)
Tabela 6 Organizatori i suorganizatori međunarodne naučno-stručne konferencije " Ekološka istina " (2010-2017)

ORGANIZER	INTERNATIONAL SCIENTIFIC AND PROFESSIONAL CONFERENCE "ECOLOGICAL TRUTH"							
	XVIII	XIX	XX	XXI	XXII	XXIII	XXIV	XXV
	Eco-Ist'10	Eco-Ist'11	Eco-Ist'12	Eco-Ist'13	Eco-Ist'14	Eco-Ist'15	Eco-Ist'16	Eco-Ist'17
University of Belgrade, Technical Faculty in Bor	X	X	X	X	X	X	X	X
Institute for Public Health - Zajecar		X	X					
Society of Young Researchers Bor	X	X	X	X	X	X	X	X
Institute of Mining and Metallurgy - Bor		X	X	X	X			X
Institute for Nature Conservation of Serbia -Belgrade		X	X		X	X	X	X
Bor Administrative District – Bor		X						
Community of Bor		X						
Touristic Organization "Bor" - Bor		X						
Students Alliance Bor - Bor		X	X		X			
West Backa Administrative District - Sombor	X							
Institute for Public Health Sombor	X							
"Vojvodina forests"Property of Sombor	X							
Regional Chamber of Commerce - Novi Sad	X							
Agriculture Professional Service - Sombor	X							
Community of Apatin	X							
Town Sombor	X							
RTB BOR Group				X				
Freeport-McMoRan Copper & Gold Inc.				X				
Rakita Exploration Bor				X				
Geoing Group Beograd				X				
British-Serbian Chamber of Commerce				X				
University of Montenegro, Faculty of Metallurgy and Technology Podgorica, Montenegro					X			
University of Zagreb, Faculty of Metallurgy Sisak, Croatia					X	X	X	X
University Christian "Dimitrie Cantemir", Faculty of Management in Tourism and Commerce Timisoara, Romania					X	X	X	X
University in Banja Luka, Faculty of Technology, Banja Luka, RS, B&H							X	
University of Pristina, Faculty of Technical Science, Kosovska Mitrovica, Serbia						X	X	X

Table 7 Venue and the Presidents of the Scientific and Organizing committees
Tabela 7 Mesto održavanja konferencije i Predsednici Naučnog i Organizacionog komiteta

Conference	Venue	President of the Scientific Committee	President of the Organizing Committee
I	Zajecar		Petar Paunovic
II	Borsko jezero	Dr Rade Kojdic	Toplica Marjanovic
III	Borsko jezero	Dr Petar Paunovic	Zvonimir Milijic
IV	Kladovo	Prof. dr Nedeljko Magdalinovic	Ljubiša Đorđevic
V	Donji Milanovac	Prof. dr Berislav Ristic	Toplica Marjanovic
VI	Negotin	Prof. dr Stevan Stankovic	Srđan Markovic
VII	Zajecar	Prof. dr Stevan Stankovic	Dušan Pejcic
VIII	Soko Banja	Prof. dr Stevan Stankovic	Nadežda Nikolic
IX	Donji Milanovac	Prof. dr Zvonimir Stankovic	Predrag Marušic

X	Donji Milanovac	Prof. dr Stevan Stankovic	Predrag Marušic
XI	Donji Milanovac	Prof. dr Stevan Stankovic	Doc. dr Radoje Pantovic
XII	Borsko jezero	Prof. dr Stevan Stankovic	Prof. dr Zoran Markovic
XIII	Borsko jezero	Prof. dr Stevan Stankovic	Prof. dr Zoran Markovic
XIV	Soko Banja	Prof. dr Stevan Stankovic	Prof. dr Milan Trumic
XV	Soko Banja	Prof. dr Stevan Stankovic	Prof. dr Milan Trumic
XVI	Soko Banja	Prof. dr Stevan Stankovic	Prof. dr Milan Trumic
XVII	Kladovo	Prof. dr Stevan Stankovic	Prof. dr Zvonimir Stankovic
XVIII	Banja Junakovic, Apatin	Prof. dr Zoran Markovic	Prof. dr Zoran Markovic
XIX	Bor	Prof. dr Zoran Markovic	Prof. dr Zoran Markovic
XX	Zajecar	Prof. dr Milan Antonijevic	Prof. dr Zoran Markovic
XXI	Borsko jezero	Prof. dr Radoje Pantovic	Prof. dr Radoje Pantovic
XXII	Borsko jezero	Prof. dr Milan Antonijevic	Prof. dr Radoje Pantovic
XXIII	Kopaonik	Prof. dr Milan Antonijevic	Prof. dr Radoje Pantovic
XXIV	Vrnjacka Banja	Prof. dr Dragana Zivkovic	Prof. dr Radoje Pantovic
XXV	Vrnjacka Banja	Prof. dr Zoran Markovic	Prof. dr Radoje Pantovic

Table 8 Number of authors and publications of papers
Tabela 8 Broj autora i objavljivanje radova

Conference	Number of authors and co-authors	Publication of papers		
		Publication	***Number of pages***	***Format***
I	*20*	*Journal "Razvitak"*	*20*	
II	*410*	*Proceedings*	*300*	*B5*
III	*260*	*Proceedings*	*678*	*B5*
IV	*250*	*Proceedings*	*510*	*B5*
V	*230*	*Proceedings*	*572*	*B5*
VI	*200*	*Proceedings*	*492*	*B5*
VII	*100*	*Proceedings*	*346*	*B5*
VIII	*260*	*Proceedings*	*728+216*	*B5*
IX	*240*	*Proceedings*	*680*	*A4*
X	*300*	*Proceedings*	*662*	*A4*
XI	*314*	*Proceedings*	*560*	*A4*
XII	*291*	*Proceedings*	*672*	*B5*
XIII	*261*	*Proceedings*	*718*	*B5*
XIV	*210*	*Proceedings*	*619*	*B5*
XV	*267*	*Proceedings*	*746*	*B5*
XVI	*272*	*Proceedings*	*664*	*B5*
XVII	*252*	*Proceedings*	*452*	*B5*
XVIII	*213*	*Proceedings*	*539*	*B5*
XIX	*240*	*Proceedings*	*687*	*B5*
XX	*245*	*Proceedings*	*649*	*B5*
XXI	*301*	*Proceedings*	*717*	*B5*
XXII	*267*	*Proceedings*	*649*	*B5*
XXIII	*356*	*Proceedings*	*797*	*B5*
XXIV	*386*	*Proceedings*	*882*	*B5*
XXV	*278*	*Proceedings*	*682*	*B5*
∑	***6423***		***15237***	

During the previous period, in these twenty-five professional and scientific meetings, including the Day of Preventive Medicine, 2915 papers were published in 30 different sections. In the section "Scientific Youth" 168 papers were published, which makes a total of 3083 papers. Also, twenty-five Proceedings (22 formats B5 and 3 A4 formats) were printed on a total of 15237 pages. The conference was attended by over 6423 authors and co-authors of papers and a large number of invitees, guests, journalists and interested individuals.

"Ecological Truth" was organized in 7 cities of Timok krajina and 3 cities outside Timok Krajina. The Organization was led by 12 Presidents of the Organizing Committee, while 10 prominent scientists chaired the Scientific Commmittees that took care about scientific and technical values of the Conference.

INSTEAD OF THE CONCLUSION

"Ecological Truth" is the only conference in this region, and wider, which has gathered all generations for the last twenty-five

years, from pupils and students to professors and foreign research workers.

A large number of experts contributed to the success of the "Ecological Truth" from the Institute and from many other institutes and faculties, the Institute for Health Care in Serbia and other organizations, such as the "Society of Young Researches".

The Society of Young Researchers Bor has been one of the permanent co-organizers of the scientific-orifessional meeting "Ecological Truth" since the first conference in 1993. Since then, the co-organizers have been changed and among the large number of new co-organizers, the Society of Young Researchers Bor is the only traditional co-organizer.

A special contribution was made by the Military Medical Academy in Belgrade with its professors Mirce Obradovic and Spiro Radulovic, prof. Stevan Stankovic from the Faculty of Geography as a long-time president of the Scientific Committee, late prof. Zoran S. Markovic from the Technical Faculty in Bor and others.

In addition to scientific-professional work, special attention was paid to accompanying activities. The goal of numerous excursions was to get acquainted with the culture and natural heritage of eastern Serbia, and later Apatin, Kopaonik, Goc and Vrnjacka Banja. Participants of the event had the opportunity to get to know the beauties of the Lazarev canyon and the Zlotska cave, the Djerdap Gorge, the Bor Lake, the Moravica canyon and the thermo-mineral springs Sokobanja. Travelling by boat, they met the values of the Danube and cultural treasures of Kladovo, Apatin. They visited the first urban settlement in Europe, "Lepenski Vir", visited Rajacke pimnice, Sokograd, Jama, Vidikovac, RTB Bor, then museums in Negotin and Zajecar, the birthplace of Stevan Mokranjac and many other cultural sights.

Finally, we can say that "(Our) Ecological Truth" has great strength. Its strength is reflected in its successful living and being held every year in the 21st century.

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RAZUMEVANJE PROBLEMA FENILKETONURIJE KROZ ISTORIJU

UNDERSTANDING OF THE PHENYLKETONURIA PROBLEM THROUGH HISTORY

Biljana Stojanović Jovanović, Stevan Jovanović

VISOKA ZDRAVSTVENA ŠKOLA STRUKOVNIH STUDIJA U BEOGRADU, BEOGRAD.

Sažetak: Fenilketonurija (PKU) je autozomno-recesivna metabolička bolest koja dovodi do mentalne retardacije i drugih neuroloških problema kada se lečenje ne započne u roku od prvih nekoliko nedelja života. Nastaje zbog nedostatka enzima fenilalanin-hidroksilaze (PAH), pa se fenilalanin nagomilava u organizmu, a smanjuje nivo tirozina. Prevelika količina fenilalanina u krvotoku dovodi do oštećenja mozga kod dece. Nedovoljna količina tirozina dovodi do smanjenja produkcije pigmenta melanina, tako da su deca sa PKU plava, nežne bele kože, sa plavim očima. Fenilalanin se u obliku fenilketona izlučuje urinom. Usled ovih ketona, znoj i urin obolelih imaju jači miris nego zdrave osobe (podseća na buđ). Gatrijev test se sprovodi kao masovna, skrining metoda za fenilketonuriju. i on je obavezni nacionalni program zdravstvene zaštite dece. Lečenje se sprovodi dijetom koja ograničava unos fenilalanina.
Ključne reči: novorođenče, fenilketonurija, skrining.

Summary: Phenylketonuria (PKU) is an autosomal recessive, metabolic disease that leads to mental retardation and other neurological problems, when treatment is not started within the first few weeks of life. It occurs due to the lack of phenylalanine hydroxylase enzyme (PAH) and phenylalanine is accumulated in the body, and the tyrosine level decreases. An excessive amount of phenylalanine in the bloodstream leads to brain damage in children. Insufficient tyrosine leads to a decrease in the production of melanin pigments, so children with PKU are blond, with soft white skin and blue eyes. Phenylalanine is excreted in the form of phenylketone in the urine. Due to these ketones, sweat and urine of sufferers have a stronger smell than of a healthy persons (resembling budding). The Guthrie test is carried out as a mass, screening method for phenylketonuria and it is a part of mandatory national child health care program. Treatment is carried out by a diet that limits the intake of phenylalanine.
Key words: newborn, phenylketonuria, screening.

UVOD

Fenilketonurija (PKU) je najčešća urođena bolest metabolizma aminokiselina. Prenosi se autozomno recesivnim putem. Bolest nastaje kao posledica nedostatka enzima fenilalanin-hidroksilaze u jetri. Enzim fenilalanin-hidroksilaza metaboliše fenilalanin u tirozin. Zbog nedostatka enzima fenilalanin- hidroksilaze, ako je enzim defektan ili nepostojeći, ova reakcija ne može da se realizuje i dolazi do nagomilavanja fenilalanina u organizmu, a smanjuje se nivo tirozina [1-6].

Prevelika količina fenilalanina u krvotoku dovodi do oštećenja mozga kod dece. Nedovoljna količina tirozina u krvotoku dovodi do smanjenja produkcije pigmenta melanina, tako da su deca plava, imaju nežno belu boju kože i plave oči [1-6]. Gen za fenilalanin-hidroksilazu nalazi se na hromozomu 12, opisan je veliki broj mutacija, njih preko 500, tako da postoji velika genotipska heterogenost oboljenja [6].

Glavne kliničke manifestacije i posledice usled visokih vrednosti fenilalanina su teška mentalna retardacija, zastoj u rastu i razvoju, epilepsija, mišićna hipertonija, tremor i drugi neurološki poremećaji. Izostaje pigmentacija u koži, očima i kosi. [7-9].

Uzimajući u obzir koncentraciju fenilalanina u krvi, razlikuje se:

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www.tmg.org.rs

- fenilketonurija (kada je koncentracija fenilalanina u krvi veća od 1200 μmol/l);
- blaži oblik fenilketonurije (kada je koncentracija fenilalanina u krvi od 600-1200 μmol/l) ; i
- blaga hiperfenilalaninemija (kada je koncentracija fenilalanina izvan referentnih granica ali je niža od 600 μmol/l) [7].

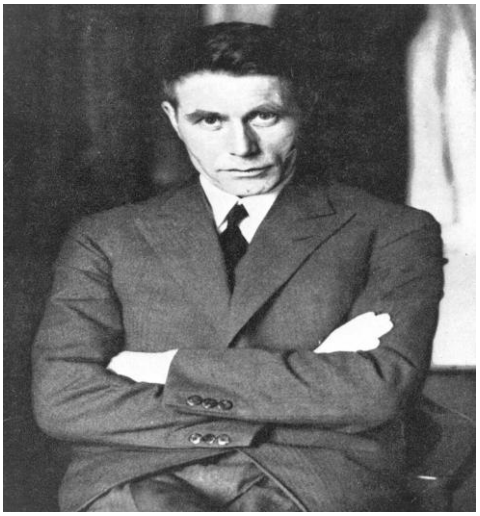
Prema svetskoj statistici ovaj poremećaj se javlja kod 1:15 000 rođenih, međutim pomenuti odnos varira od regiona do regiona. Incidencija fenilketonurije u beloj rasi u proseku iznosi od 1: 10 000 do 1: 20 000 rođenih. Prosečna incidencija ovog oboljenja u Evropi je 1:10 000, najveća učestalost je u Turskoj (1: 2 600) i Irskoj (1: 4 500) a najmanja u Finskoj gde iznosi 1:100 000 [10-12]. Incidencija klasične fenilketonurije na teritoriji Srbije je između 1: 18 732 i 1: 39 338, što nas svrstava u zemlje sa srednjim incidencijom PKU u svetu, ali niže od prosečne incidencije u Evropi, koja iznosi između 1: 10 000 i 1: 20 000 [9].

Primena dijete siromašne fenilalaninom sprečava loš ishod bolesti i omogućava normalan život obolelih osoba, ali sa dijetom se mora početi najkasnije do kraja prvog meseca života[13].

NAJRANIJI OPIS

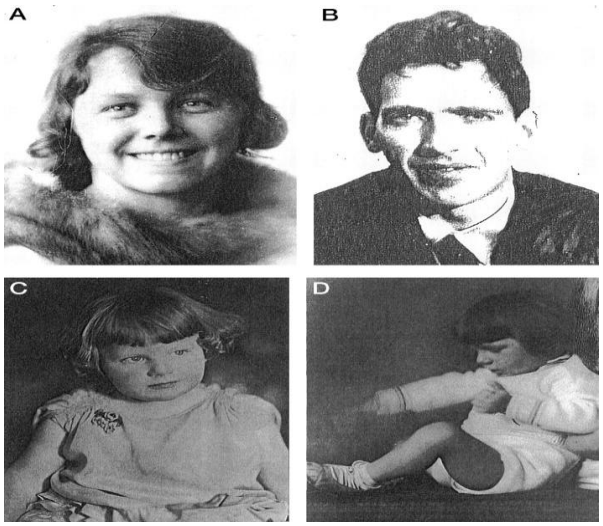
U medicinsku literaturu pojam nasledne metaboličke bolesti, uveo je engleski lekar Archibald Edward Garrod 1908 godine [14]. On je uočio da je bolest urođena i češća kod bliskih srodnika pa je na osnovu toga zaključio da je nasledna. Svoja istraživanja objavio je u radu Urođene bolesti metabolizma (Inborn errors of metabolism.) koji je objavljen 1909. godine [15]. Fenilketonuriju je prvi put opisao norveški lekar i naučnik Ivar Asbjorn Foling 1934. godine (slika 1).

Slika 1. Ivar Asbjorn Folling
Picture 1. Ivar Asbjörn Fölling



Doktoru Folingu, koji je u tadašnje vreme bio na dobrom glasu kao poznavalac biohemije, obratila se jedna majka dvoje mentalno zaostale dece nakon dugotrajnog obilaženja i traženja pomoći jer je htela da sazna, da li je čudan miris urina njene dece povezan sa njihovom mentalnom zaostalošću. Devojčica je imala šest godina, znala je da izgovori samo nekoliko reči, imala je tipične znake spastične paralize sa uobičajenim teškoćama u kretanju. Mlađi brat od četiri godine nije govorio niti hodao, nije pratio pogledom predmete oko sebe i nije kontrolisao stolicu i mokrenje (slika 2).

Slika 2. „Prva“ PKU porodica
Picture 2. The “First” PKU Family



Foling je analizirao njihov urin koristeći rastvor feri-hlorida, očekujući da će dobiti crveno-braon boju karakterističnu za ketone. Kod malih pacijenata čiji je urin doktor pregledao primetilo se da je mokraća poprimila tamno zelenu boju za koju se zna da potiče od fenilpiruvata, metabolita fenilalanina [16, 17]. Prvi zaključak je bio da dvoje dece, sestra i brat sa umnom zaostalošću izlučuju u mokraći nešto čega nema kod zdrave dece. Pitanja koja su se nametnula: izlučuju li sva mentalno zaostala deca takvu mokraću i koji je hemijski sastav mokraće te dece? Odgovor na ova pitanja otkriva novu bolest, za koju je dr Foling predložio naziv „fenilpiruvična idiotija“, time se želelo istaći da je reč o bolesti praćenoj mentalnom retardacijom uz koju bolesnici izlučuju fenilpiruvičnu kiselinu u mokraći [18]. Nekoliko godina kasnije, Penrose i Quastel menjaju ime bolesti u „fenilketonurija“ čiji se naziv zadržao do danas [19]. Dr Folling nažalost nije mogao pomoći oboleloj deci, ali je svojim otkrićem učinio prvi veliki korak, jer je povezao hemijske promene u mokraći obolele dece sa naslednim oblikom umne zaostalosti [18]. On je nakon detaljne hemijske analize urina mentalno retardiranih brata i sestre, zatražio od svih lekara u blizini Osla da detaljno analiziraju urin pacijenata koji imaju bilo kakav oblik mentalne retardacije. Ista analiza u mokraći je urađena kod 430 osoba sa mentalnom retardacijom do tada nepoznatog uzroka i kod osam osoba dobijen je isti rezultat kao kod dvoje opisane dece. Dr Folling je primetio da ovi bolesnici pored mentalne retardacije imaju i druge sličnosti a to su; prisustvo ekcema, niski rast, široka ramena i spastičan hod. Ispitivanjem porodičnog stabla došao je do zaključka da je u pitanju autozomno recesivno nasleđivanje [3].

Nakon trideset godina od kako je opisana biohemijska osnova ove bolesti, došlo se do zaključka da ishrana sa ograničenim unosom fenilalanina može da spreči mentalnu zaostalost, pre nego što se simptomi bolesti pojave [19].

Kod bolesnika sa fenilketonurijom, Dr Horst Bickel 1954. godine dokazao je da ishrana siromašna fenilalaninom može da smanji njegovu koncentraciju u organizmu i spreči razvoj mentalne retardacije. Dr Willard Centerwall iz Los Angelesa započeo je 1957. godine "test vlažnih pelena", prvi korak ka masovnom pregledu za fenilketonutiju. Više nije bilo potrebno da se sakupljaju uzorci urina i zatim šalju u dijagnostičku laboratoriju. Pedijatri su sada mogli da izvedu ovaj test u svojim ordinacijama. Dr Centerwall je razvio "test pelena" tako što je feri-hlorid dodavao vlažnim pelenama pa ako se urin oboji zeleno, to je bio

znak da postoji fenilketonurija. Ova smanjena potreba za slanjem urina u laboratorije za dijagnostiku je omogućila lekarima u primarnoj zdravstvenoj zaštiti da sami testiraju bebe. One su mogle biti testirane već u 5-6 nedelji života, što je dovoljan period da se fenilpiruvična kiselina stvori u organizmu obolelih od fenilketonurije. Tako je počeo masovni skrining na fenilketonuriju. Nešto kasnije, 1961. godine Dr Willard Centerwall je prikazao pozitivne rezultate dijetetskog tretmana 10 odojčadi i male dece sa fenilketonurijom sa niskim fenilalanin unosom (Lofenalac) uzrasta od 6 meseci do 3 godine[19, 20].

POČECI SKRININGA NA FENILKETONURIJU

Šezdesetih godina prošlog veka, pojava programa skrininga novorođenčadi predstavljala je pravu malu revoluciju u preventivnoj medicini. Danas su takvi programi širom sveta opšte prihvaćeni. Da bi se neka bolest uvrstila u program sistemskog traganja, a da za to postoji i javno zdravstveno opravdanje potrebni su odredjeni uslovi[20].

Ishrana siromašna fenilalaninom može da smanji koncentraciju fenilalanina i spreči razvoj mentalne retardacije kod bolesnika sa fenilketonurijom. Najbolji rezultati se postižu kada se sa dijetom počne u prvom mesecu života kako je dokazao Bickel ranih pedesetih godina prošlog veka [20, 21]. Gatri je početkom šezdesetih godina prošlog veka ustanovio da se jednostavnom metodom bakterijske inhibicije, iz uzorka krvi na filter papiru, može odrediti koncentracija fenilalanina (slika 3). [22].

Slika 3. Robert Gatri
Picture 3. Robert Guthrie

Ovo otkriće je otvorilo put ranom, neonatalnom otkrivanju bolesti. Skrining na fenilketonuriju u SAD počinje 1962. godine [23]. Kod nas skrining počinje u Dubrovniku 1966. godine, kada je organizovan na inicijativu Ministarstva zdravlja SAD-a, nakon što je Američka vlada odobrila novac za izvođenje 100 000 skrining testova u nekoliko većih porodilišta tadašnje Jugoslavije [24]. Program je vođen iz Instituta za zdravstven zaštitu majke i deteta Republike Srbije „Dr Vukan Čupić“ u Beogradu i bilo je otkriveno i uspešno lečeno desetoro dece sa ovim problemom. Tačni zapisi o rezultatima nisu dostupni, a nakon što su sredstva potrošena, prestao je sistematski rad u ranom otkrivanju fenilketonurije kod novorođenčadi. Važno je bilo da se šira javnost upoznala sa problemom fenilketonurije. Pilot program na teritoriji tadašnje Jugoslavije sproveli su Vulović i saradnici 1967. godine, dok organizovani skrining na ovu bolest u Srbiji počinje da se sprovodi od 1983. godine [25].

NEONATALNI SKRINING NA FENILKETONURIJU U POSLEDNJOJ DEKADI XX VEKA

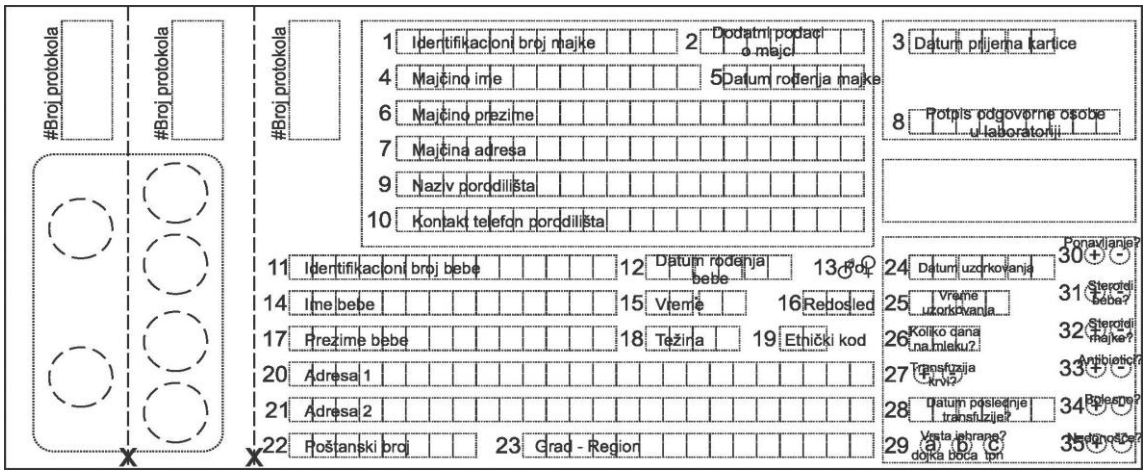
Novorođenački skrining je postupak u okviru preventivne medicine kojem je svrha rano otkrivanje bolesne novorođenčadi kod koje

će pravovremena dijagnoza i lečenje dovesti do značajnog smanjenja smrtnosti, morbiditeta i invalidnosti. Uzorak krvi treba uzeti svakom novorođenčetu.

Neonatalni skrining podrazumeva program ispitivanja celokupne populacije novorođenčadi neke zemlje ili regiona na nasledne bolesti koje je moguće lečiti, a koje imaju latentni period do kliničkog ispoljavanja. Neonatalni skrining program je pod pokroviteljstvom države i regulisan je Zakonom o zdravstvenoj zaštiti ("Uredbom o nacionalnom programu zdravstvene zaštite žena, dece i omladine"). Kriterijumi koje određena bolest mora da zadovolji da bi se uključila u nacionalni neonatalni skrining su kriterijumi Wilsona i Jungera iz 1968. godine, a koje je 1975. godine prihvatila Svetska zdravstvena organizacija [26].

Fenilketonurija je oboljenje kod koga se veoma uspešno sprovodi masovni neonatalni skrining koji je u našoj zemlji zakonski regulisan. Da bi se organizovao masovni neonatalni skrining za određenu bolest, potrebno je da budu zadovoljeni sledeći uslovi: da je oboljenje relativno često; da ne postoje bilo kakve kliničke abnormalnosti na osnovu kojih se data bolest može dijagnostikovati u ranom neonatalnom uzrastu; da postoji senzitivan i specifičan skrining test;da je datu bolest moguće efikasno lečiti [27, 28]. Test za dijagnostikovanje bolesti fenilketonurija je Gatrijev test [29] i zasniva se na analizi osušene kapi krvi uzete iz pete novorođenčeta (Slika 4).

Slika 4. Kartica za neonatalni skrining
Picture 4. Screening card



Na agaroznu ploču se stavlja mali krug filter papira sa osušenom kapi krvi i ukoliko je povećana koncentracija fenilalanina, fenilpiruvata i fenilacetata doći će do rasta bakterija na agaroznoj ploči. Metoda je jednostavna, rezultati su dostupni za 24 sata, ima malu grešku merenja i jeftina je (cena jednog Guthrie testa je oko 2 evra) [9, 30].

SPROVOĐENJE SKRININGA NA FENILKETONURIJU DANAS

Skriningom su obuhvaćena sva novorođena deca. Uzoroci krvi za skrining uzimaju se na skrining karticama u porodilištu i/ ili na neonatološkim odeljenjima gde je dete rođeno ili u bolničkim ustanovama ukoliko je novorođenče zbog bolesti bilo hospitalizovano. Za novorođenčad u intenzivnoj i poluintenzivnoj nezi skrining se odlaže do 10. dana života i uzima se još jedan uzorak pre otpusta. Kod prevremeno rođene dece prvi uzorci za skrining uzimaju se najkasnije do 10- og dana života, a potom se uzimanje uzoraka ponavlja u drugoj nedelji života. Ako novorođenče ne toleriše ishranu, sa prvim uzorkom se šalje i napomena da novorođenče nije na oralnoj ishrani. Drugi uzorak se uzima kada novorođenče postigne enteralni unos u trajanju od 48 sati. Ukoliko novorođenče mora da dobije transfuziju krvi, prvi uzorak se uzima pre transfuzije, a drugi u uzrastu od sedam dana ili pre otpusta [31, 32].

Roditelji moraju imati blagovremenu i potpunu informaciju o sprovođenju metaboličkog skriniga kod njihovog novorođenčeta. Kod novorođenčadi sa pozitivnim rezultatom lečenje na fenilketonuriju počinje već odmah po dobijanju rezultata i to doživotnim ograničavanjem oralnog unosa fenilalanina. Da bi se to postiglo koriste se fabrički preparati mleka sa smanjenom količinom fenilalanina [31, 32].

FENILKETONURIJA SE LEČI DIJETOM

Osnova lečenja klasične fenilketonurije je sprovođenje striktne, niskoproteinske dijete, sa smanjenim, kontrolisanim unosom fenilalanina. Da bi se sprečile teške posledice, dijetu je neophodno početi što ranije, u prvim nedeljama života deteta [31, 32]. Stavovi o neophodnom trajanju ovakvog načina ishrane tokom vremena su se menjali. Dijeta je najstroža u prvim godinama života kada je i razvoj deteta najintenzivniji. Ranije je smatrano da je dovoljno dijetu sprovoditi do šeste godine života. Postepeno je ta granica pomerana ka starijem uzrastu.

Danas je generalni stav da dijetu treba sprovoditi doživotno, s tim što je ona liberalnija nakon adolescencije [33]. Osnovni princip dijete je da se unos prirodnih proteina ograniči, a veći deo proteinskih potreba zadovolji iz proteinskih preparata koji ne sadrže fenilalanin. Mesečno, u proseku, za jedno dete predškolskog uzrasta izdvaja se oko 340 evra dok je suma koju treba izdvojiti za starije dete oko 635 evra. Ove svote su velike i predstavljaju ogroman teret za budžet porodica [10].

ZAKLJUČAK

Deca obolela od fenilketonurije (PKU) pre uvođenja neonatalnog skrininga bila su lišena svih mogućnosti za vođenje normalnog života. Lečenje treba započeti što pre, čim se bolest otkrije a nažalost ono traje doživotno. Uz pravovremeno započeto lečenje (u prvim nedeljama života) i redovno, tačno i neprekidno sprovođenje lečenja i kontrole, dete ima odlične izglede da se razvija i raste, te se ni po čemu neće razlikovati od svojih vršnjaka. Svaki prekid lečenja i zanemarivanje redovne kontrole neminovno dovodi do porasta fenilalanina u krvi sa svim posledicama. Unapređenje dijagnostike, nege i lečenja kao i sveobuhvatnog kvaliteta života obolelih od fenilketonurije zahteva angažovanje svih činilaca zdravstvenog sistema Republike Srbije. Za uspešno lečenje fenilketonurije zaslužni su zdravstveni profesionalci koji postavljaju dijagnozu kroz neonatalne skrining programe, pedijatri, medicinske sestre dijetetičari i osobe koje nadgledaju tretman lečenja fenilketonurije.

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Koristite font Times New Roman, veličine 12 p. Paragraf pišite tako da se ravna samo leva ivica (Alignment left). Ne delite reči na slogove na kraju reda. Ubacite samo jedno prazno mesto posle znaka interpunkcije. Ostavite da naslovi i podnaslovi budu poravnati uz levu ivicu. Koristite podebljana (bold) slova, kurziv (italic), sub i superscript i podvučena slova samo gde je to neophodno. Tabele, slike i grafikone možete umetnuti u tekst na mestu gde treba da se pojave u radu. Prihvatljvi formati za tabele, grafikone, ilustracije i fotografije su doc, xls, jpeg, gif i npg.

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Originalni rad je sistematski obavljeno istraživanje nekog problema prema naučnim kriterijumima i jasnim ciljem istraživanja. Dužina teksta je ograničena na 3500 reči, maksimalno 5 tabela, grafikona, ili slika (do 12 stranica teksta).

Pregledni članak obuhvata sistematski obrađen određeni medicinski problem, u kome je autor ostvario određeni doprinos, vidljiv na osnovu autocitata. Pregledni članak se obično naručuje od strane uredništva, ali se razmatraju i nenaručeni rukopisi. Kontaktirajte uredništvo pre pisanja preglednog članka. Dužina teksta može biti do 5000 reči (18 stranica).

Prikaz bolesnika rasvetljava pojedinačne slučajeve iz medicinske prakse. Obično opisuje jednog do tri bolesnika, ili jednu porodicu. Tekst se ograničava na 2500 reči, najviše 3 tabele, ili slike i do 25 referenci (ukupno do 5 stranica teksta).

Člancima iz istorije medicine i zdravstvene culture rasvetljavaju se određeni aspekti medicinske prakse u prošlosti. Dužina teksta može biti do 3500 reči (12 stranica).

Objavljuju se i kratki prilozi iz oblasti medicinske prakse (dijagnostika, terapija, primedbe, predlozi i mišljenja o metodološkom problem itd), kao i prikazi sa različitih medicinskih sastanaka, simpozijuma i kongresa u zemlji i inostranstvu, prikazi knjiga i prikazi članaka iz stranih časopisa (do 1000 reči, 1–2 tabele ili slike, do 5 referenci (do 3 stranice teksta).

Pisma redakciji imaju do 400 reči, ili 250 reči ukoliko sadrže komentare objavljenih članaka.

Po narudžbini redakcije, ili u dogovoru sa redakcijom objavljuju se i radovi didaktičkog karaktera.

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Tekst rada sadrži u prvom redu naslov rada na srpskom jeziku, u drugom redu naslov rada na engleskom jeziku, u narednim redovima: puna imena i prezimena autora i svih koautora; naziv, mesto i adresu institucija iz kojih je autor i koautori (brojevima u zagradi povezati imena autora); eventualnu zahvalnost za pomoć u izradi rada; predlog kategorije rukopisa (originalni rad, pregledni članak, prikaz bolesnika i dr); ime i prezime, godinu rođenja autora i svih koautora; punu adresu, broj telefona i faksa, kao i e-mail autora za korespondenciju. Sledi sažetak na srpskom jeziku (najbolje do 300 reči). Sažetak ne može imati fusnote, tabele, slike, niti reference. Sažetak treba da sadrži cilj istraživanja, materijal i metode, rezultate i zaključke rada i treba da bude napisan u jednom paragrafu, bez podnaslova. U njemu ne smeju biti tvrdnje kojih nema u tekstu članka. Mora biti napisan tako da i obrazovani nestručnjak može iz njega razumeti sadržaj članka. Posle sažetka napisati 3 do 8 ključnih reči na srpskom jeziku. Nakon sažetka na srpskom jeziku, napisati sažetak na engleskom jeziku (Summary) kao doslovan prevod sažetka na srpskom i 3 do 8 ključnih reči na engleskom jeziku (key words). Sledi uvod (sa istoimenim podnaslovom) koji mora biti kratak, sa kratkim pregledom literature o datom problemu i sa jasno izloženim ciljem članka u posebnom paragrafu na kraju uvoda. Poglavlje o materijalu i metodama (sa istoimenim podnaslovom) mora sadržati dovoljno podataka da bi drugi istraživači mogli ponoviti slično istraživanje bez dodatnih informacija. Imena bolesnika i brojeve istorija bolesti ne treba koristiti, kao ni druge detalje koje bi pomogli identifikaciji bolesnika. Treba navesti imena aparata, softvera i statističkih metoda koje su korišćene. Rezultate (sa istoimenim podnaslovom) prikažite jasno i sažeto. Ne treba iste podatke prikazivati i u tabelama i na grafikonima. U diskusiji (sa istoimenim podnaslovom) treba raspravljati o tumačenju rezultata, njihovom značenju u poređenju sa drugim, sličnim istraživanjima i u skladu sa postavljenim hipotezama istraživanja. Ne treba ponavljati već napisane rezultate. Zaključke (sa istoimenim podnaslovom) treba dati na kraju diskusije, ili u posebnom poglavlju.

Svaka tabela, grafikon, ili ilustracija mora biti razumljiva sama po sebi, tj. i bez čitanja teksta u rukopisu. Iznad tabele, grafikona, ili slike treba da stoji redni broj i naslov. Legendu staviti u fusnotu ispod tabele, grafikona, ili slike i tu objasniti sve nestandardne skraćenice. Ilustracije (slike) moraju biti oštre i kontrastne, ne veće od 1024x768 piksela. Broj slika treba ograničiti na najnužnije (u principu ne više od 4–5). Ukoliko se slika, tabela, ili grafikon preuzima sa interneta, ili nekog drugog izvora, potrebno je navesti izvor. Naslove i tekst u tabelama, grafikonima i tekstu i slike dati na srpskom i na engleskom jeziku.

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Organizacija kao autor:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Efect of brestfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

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American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http://www.ama-assn.org/ama/pub/category/1736.html

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Luk Filds
Doktor, 1891
(The Doctor)
Ulje na platnu
Galerija Tejt, London

Od umetnika Luka Fildsa 1890. godine Ser Henri Tejt naručio je sliku ostavivši slikaru slobodu u izboru teme. Umetnik je pri stvaranju ovog dela imao na umu tragičan događaj iz sopstvenog života – smrt svog jednogodišnjeg sina. Bez obzira na tragediju, Filds je bio impresioniran predanošću i zalaganjem doktora koga je tada imao prilike da gleda očima oca bolesnog deteta. Iako doktor na slici dosta podseća na samog umetnika, nekoliko različitih ljudi poslužilo je kao model za lekara. Na ovaj način Filds je želeo da predstavi doktora tog vremena; kroz lik doktora želeo je da prikaže samu suštinu lekarske profesije, a ne konkretnu ličnost.
U vreme nastajanja slike, u umetnosti je bio je popularan socijalni realizam koji prikazivao težinu života radničke klase.U tom duhu nastala je i slika Doktor na kojoj možemo videti jedan skromno namešten ribarski dom sa posudjem od kalaja, sa istrošenim tepihom na kamenom podu, sa iznošenom odećom roditelja.

Centralne figure na slici svakako su bolesno dete koje leži na improvizovanom ležaju sačinjenom od dve spojene stolice i zabrinuti lekar koji pažljivo i strpljivo posmatra pacijenta. U pozadini, kao u imaginarnoj čekaonici, prikazani su roditelji deteta. Otac stoji, sa jednom rukom na ramenu svoje žene koja daje nemu podršku, nepomičnog pogleda uprtog u doktora. Majka deteta iscrpljena nepodnošljivom brigom skrivenog lica ruke drži sklopljene za molitvu. Svako od njih, na svoj način, očekuje bilo kakav znak od strane doktora. Doktor sedi pored bolesnog deteta u napetom položaju, zaleđen izmedju spremnosti da reaguje (oslonjena ruka na koleno) i odlučnosti da istraje (brada oslonjrena na dugu ruku). Njegov položaj i pogled uprut u bolesno dete odražava svu predanost ne samo svojoj profesiji već pacijentu. Lečenje, tj medicina je prisutna u ovoj prostoriji, na stolu je poluprazna bočica sa lekom, tu je i lavor i bokal sa vodom za spuštanje temperature, na podu je recept. Ali napetost cele kompozicije, emotivni naboj koji zrači iz prikazane situacije, ukazuju na suštinu odnosa doktora prema malom pacijentu čiji je život u njegovim rukama. Nagoveštaj olakšanja vidi se u slabom svetlu koje se probija kroz prozor iza roditelja, nagoveštavajući da je najgori deo noći prošao, i da zora, koja simbolizuje olakšanje upravo stiže.

Tihi heroizam običnog doktora ukazuje da heroji nisu oni koji čine neverovatne velike stvari, već oni koji predano radeći svoj svakodnevni posao čine ono za šta su se spremali da čine.

Ada Vlajić,
Istoričar umetnosti