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FETAL NEUROSONOGRAPHY AND FETAL BEHAVIOUR
FETALNA NEUROSONOGRAFIJA I FETALNA PONAŠANJA

Snežana Rakić[1,2]

Summary

The ultrasonographic monitoring of fetal neural development is one of the most important objectives in perinatal medicine. The aim of this study was to monitor neurological development and analyse fetal behaviour by using 4D ultrasound. We conducted a prospective study of 150 singleton pregnancies in order to monitor neurological development and analyse fetal behaviour by using 4D ultrasound. The study was done by using ultrasound machine MEDISON ACCUVIX XQ transvaginal and transabdominal 5MHz sound with Doppler flow. Fetal movements in the first trimester and fetal facial expressions in the third trimester were analysed. In the first trimester, tests were conducted in the 8th, 12th and 14th week of pregnancy. Embryonic/fetal activity in the first trimester begins with movements that represent the functional expression of early neonatal activity. Identification of first reflexes is a measure of neurological development in the second and third trimester of pregnancy. Development of the central nervous system is a complex process and it is reflected in the complexity of motor, sensory, cognitive and affective functions and patterns of behaviour. Fetal behavioural patterns correlate with the development of central nervous system, while the quality of fetal movements reveals the integrity of central nervous system. For the assessment of fetal brain function a prenatal neurological test (KANET) can be used. 4D ultrasound represents an important advancement in monitoring fetal neurological development and behaviour.

Keywords: central nervous system, fetal behaviour, four-dimensional ultrasound, KANET

Sažetak

Ultrasonografsko praćenje neurološkog razvoja fetusa je jedan od najznačajnijih ciljeva u perinatalnoj medicini. Cilj ovog rada je bio ispitivanje neurološkog razvoja i analiza fetalnih ponašanja korišćenjem 4D ultrazvuka. Sproveli smo prospektivnu studiju na 150 jednoplodnih trudnoća radi praćenja neurološkog razvoja i analize fetalnih ponašanja korišćenjem 4D ultrazvuka.Ispitivanje je rađeno upotrebom ultrazvučnog aparata Medison ACCUVIX XQ transvaginalnom i transabdominalnom sondom snage 5 MHz sa Dopler protokom. Analizirani su fetalni pokreti u prvom trimestru i ekspresija fetalnog lica u trećem trimestru. U prvom trimestru ispitivanja su vršena u osmoj, dvanestoj i četrnestoj nedelji trudnoće.Embrionalna/ fetalna aktivnost u prvom trimestru trudnoće počinje pokretima koji predstavljaju funkcionalnu ekspresiju rane neonatalne aktivnosti. Prepoznavanje prvih refleksa je mera neurološkog razvoja u II i III trimestru trudnoće.Razvoj centralnog nervnog sistema je kompleksan proces i odražava se u kompleksnosti motornih, osetnih, kognitivnih i afektivnih funkcija i obrazaca ponašanja. Obrazci fetalnog ponašanja koreliraju sa razvojem centralnog nervnog sistema a kvalitet fetalnih pokreta otkriva integritet centralnog nervnog sistema.Za procenu funkcije fetalnog mozga može se koristi prenatalni neurološki test (KANET). 4D ultrazvuk predstavlja značajan napredak u praćenju fetalnog neurološkog razvoja i ponašanja.

Ključne reči: centralni nervni sistem, fetalno ponašanje, 4D ultrazvuk, KANET

Uvod

Ultrasonografsko praćenje neurološkog razvoja fetusa je jedan od najznačajnijih ciljeva u perinatalnoj medicini.Fetalno ponašanje predstavlja fetalnu aktivnost detektovanu ultrazvučnim pregledom. Analiza fetalnog ponašanja doprinosi proceni neurološkog razvoja fetusa. Za ispitivanje morfološkog razvoja embriona i fetusa kao i fetalnih ponašanja najveći značaj ima primena 3D i 4D ultrazvuka (1). Spontana fetalna aktivnost u preterminskih i terminskih fetusa bi mogla biti indikator fetalne disfunkcije u ranim fazama fetalnog razvoja. Kardinalni pokreti fetusa su najčešći i najkompleksniji pokreti i oni su mera fetalne neurološke maturacije (2). U više izvedenih studija ispitivani su razvoj fetalnih pokreta i neurološki razvoj (3). Fetalno ponašanje predstavlja fetalnu aktivnost detektovanu ultrazvučnim pregledom. Analiza fetalnih ponašanja doprinosi proceni normalnog i patološkog neurološkog fetalnog razvoja. Uvođenje 3D i 4D ultrazvučne tehnologije omogućila je bolju vizuelizaciju fetalne anatomije i fetalnog ponašanja in utero (4). Sa napredovanjem gestacijske starosti trudnoće fetalni kvantitativni i kvalitativni obrasci ponašanja postaju sve složeniji. Sporadični pokreti tela fetusa se menjaju u dobro organizovane obrasce ponašanja (5). Iako danas postoje savremene visokotehnološki razvijene ultrasonografske tehnike, nije uvek moguće direktno analizirati funkcionalni razvoj fetalnog nervnog sistema.

Cilj rada

Cilj tada je bio procena neurološkog razvoja embriona i fetusa na osnovu praćenja njihovog morfološkog razvoja i analize fetalnih ponašanja.

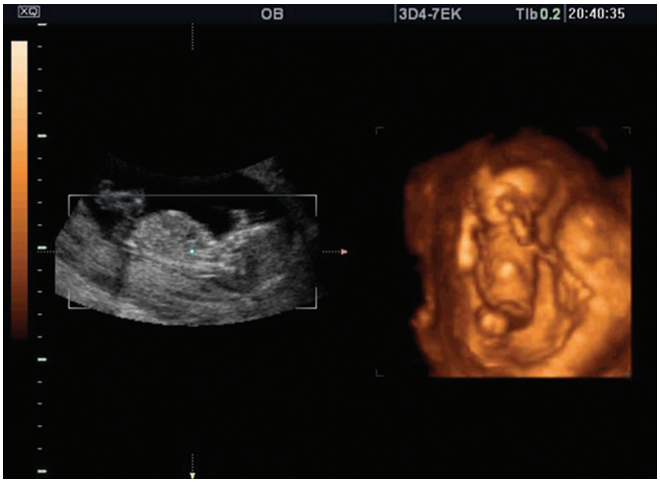
Materijal i metode

Ispitivanje predstavlja prospektivnu studiju sprovedenu na 150 trudnica sa jednoplodnom trudnoćom, radi pra-

ćenja neurološkog razvoja i analize fetalnih ponašanja. Ispitivanje je vršeno korišćenjem 2D i 4D ultrazvuka. 4D ultrazvučno ispitivanje je rađeno na ultrazvučnom aparatu Medison ACCUVIX XQ, transvaginalnom i transabdominalnom sondom snage 5MHz sa Dopler protokom. Transvaginalni 4D kolor Doppler ultrazvuk smo koristi osim za ispitivanje morfologije embriona i fetusa i za funkcionalno hemodinamsko ispitivanje fetalnog cerebrospinalnog krvnog protoka u prvom trimestru. Posle 10 nedelje trudnoće koristili smo transabdominalni 4D ultrazvuk zbog veće mogućnosti ispitivanja fetalnih pokreta. Analizirani su fetalni pokreti u prvom trimestru trudnoće i fetalna ponašanja u II i III trimestru trudnoće. Vreme pregleda je bilo između 12 i 17.30h bez uzimanja obroka hrane 2h pre ispitivanja. U prvom trimetstru ispitivanja su vršena u 8, 12 i 14 nedelji trudnoće. Za analizu fetalnih ponašanja u II i III trimestru trudnoće ispitivane trudnice su bile podeljene u grupu trudnoća niskog rizika (77 trudnica) i grupu trudnoća visokog rizika (73 trudnice). Grupu trudnoća visokog rizika sačinjavalo je 30 trudnica sa preterminskom prevremenom rupturom plodovij ovojaka, 11 trudnica sa postterminskom trudnoćom i 32 trudnice sa gestacijskim dijabetes melitusom. Za procenu stanja fetalnog centralnog nervnog sistema upotrebom 4D ultrazvuka koristili smo Kurjakov antenatalni neurološki test (Kurjak Antenatal Neurodevelopmental Test) - KANET iz 2008 godine (6). Ovaj test smo izvodili u trećem trimestru trudnoće između 28 i 38 nedelje trudnoće. Ispitivanje ovim testom traje oko 20 minuta. Parametri KANET testa su: izolovana antefleksija glave, kranijalne suture, cirkumferencija glave, izolovano treptanje oka, promene lica, otvaranje usana, izolovani pokreti ruke, izolovani pokreti noge, položaj palca, Gestelt percepcija o fetalnim generalizovanim pokretima. Svaki pojedinačni fetalni parametar i znak se boduju. Normalni fetusi imaju KANET skor između 14-20, što predstavlja skor optimalnog neurološkog razvoja. Fetusi sa potencijalnim neurološkim abnormalnostima imaju skor od 5-13. Fetusi koji su neurološki abnormalni imaju prenatalni skor od 0-5. U slučaju postojanja neurološki abnormalnog testa, on se ponavlja svake dve nedelje do porođaja. Dobijeni podaci su statistički obrađeni korišćenjem metoda analitičke statistike: studentov t-test i X^2 test.

Rezultati

U našem ispitivanju detekcija trudnoće 2D ultrazvukom u 3-4 nedelji trudnoće zasnivala se na opažanju: decidualne reakcije, intradecidualnog znaka, i postimplantacionog krvavljenja. U 5 nedelji trudnoće bio je vidljiv gestacioni mešak, a žumačna kesa je bila vidljiva kao znak duplog prstena.U 5,5 nedelji trudnoće detektuje se embrion sa srčanom radnjom. U 7-9 nedelji vidljiv je embrion, centralni nervni sistem i amnionske membrane.2D ultrazvukom je u 7. nedelji merena dužina embriona tj rastojanje teme-trtica (TT) koje je iznosi lo oko 12mm,vizuelizuje se fetalna glava i neuralna cev. U 8 nedelji dužina ploda je dužine 15mm, vizuelizuje se centralni nervni sistem sa svojim elemenatima i to: rombencefalon, prozencefalon i mezencefalon. Duž stražnje strane embriona moguće je videti osifikacione tačke-jedra medule spinalis tj neuralne cevi. U 10 nedelji trudnoće bile su vidljive bočne komore sa pleksus horoideusom i falks cerebri (Butterfly znak). U 12 nedelji vidljiva je medula spinalis, bočne komore, falks cerebri i cerebelum. Izgled fetusa u 13. nedelji trudnoće posmatran 4D ultrazvukom prikazan je na slici 1.



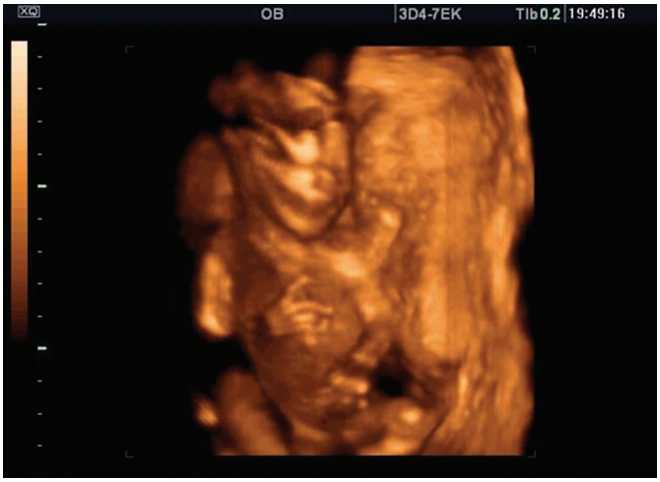
Slika 1. Fetus u 13 nedelji trudnoće, 4D ultrazvuk

Distribucija embrionalnih i fetalnih pokreta u I trimestru trudnoće u našem ispitivanju prikazana je na tabeli br 1.

Prepoznavanje prvih refleksa je mera neurološkog razvoja u drugom i trećem trimestru trudnoće od kojih su refleks hvatanja i mogući Moro refleks dva najznačajnija. U 11,4 nedelji trudnoće registrovali smo da fetus hvata pupčanu vrpcu, ako ona dođe na palmarnu stranu šake, to je palmarni refleks hvatanja pupčane vrpce. Ovo smo videli kod >95% fetusa pri ispitivanju između 11,2 – 11,5 nedelja trudnoće. Ovaj refleks je trajao oko 4 minuta. Prvi fetalni refleksi prikazani su na slici 2.

Tabela 1. Distribucija pokreta embriona i fetusa u I trimestru trudnoće

Vrsta pokreta	Gestacijska starost trudnoće u nedeljama	Dužina trajanja u sekundama	Viđeni ultrazvukom % fetusa
Prvi embrionalni pokreti	7,4	2	80
Generalizovani pokreti	8,3	5	90
Istezanje	10	3	82
Štucanje	9	3	95
Otvaranje usta	10,5	1,5	82
Disajni pokreti	10,5	5	92
Pokreti ruke prema glavi	10	1,5	98
Rotacija glave	10	2	98
Gutanje	12	1	94,3

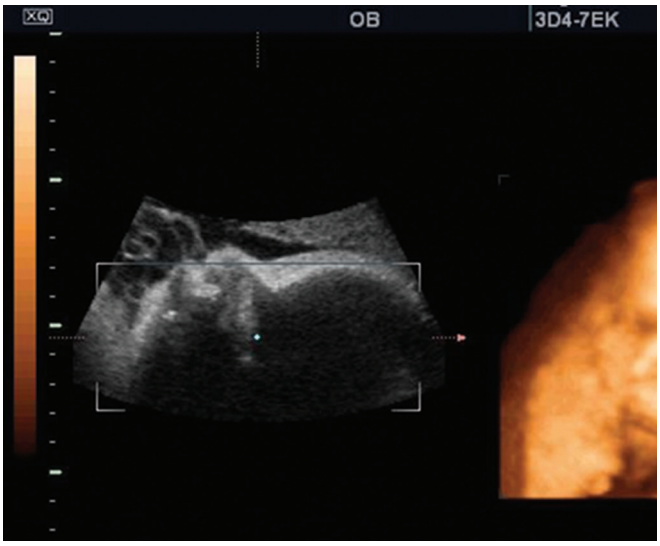


Slika 2. Prvi fetalni refleksi, 4D ultrazvuk

Fetalno ponašanje u drugom i trećem trimestru trudnoće

Kada su u pitanju fetalna ponašanja u II trimestru u našem uzorku diferenciraju se dve grupe pokreta: veliki pokreti gornjih ekstremiteta kao i facijalne ekspresije. Pokret otvaranja očiju fetusa smo detektovali najranije u 20 nedelji gestacije. U 34 nedellji trudnoće registrovali smo brze ili spore pokrete očiju fetusa. Za ova ispitivanja su bila neophodna 4D ultrazvučna ispitivanja jer se njima obezbeđuje kvantitet i kvalitet pokreta fetalne facijalne ekspresije.

U trećem trimestru održava se refleks hvatanja, a analiziraju se pokreti gornjih ekstremiteta prema glavi, pokreti šaka prema glavi, ustima, oku, licu i uhu, pokreti glave (izolovana retrofleksija glave i izolovana rotacija glave), kao i izraz lica (izolovano žmirkanje, zatvaranje i otvaranje očiju, zevanje, plaženje jezika, pućenje usta, sisanje i gutanje). Postoji longitudinalno smanjenje incidence ovih pokreta kako gestacija napreduje kao i njihovo ciklično smenjivanje u periodu od 36-40 nedelje trudnoće. Ponašanje fetusa u III trimestru prikazano je na slici 3.



Slika 3. Ponašanje fetusa u III trimestru, 4D ultrazvuk

U grupi trudnica sa 40+6 nedelja trudnoće nađena je veća incidenca pokreta zevanja fetusa nego u grupi trudnica od 37- 40 nedelja trudnoće, $p<0.05$. Pokreti zevanja nisu do sada kompletno objašnjeni. Oni su pokrenuti aktivnošću nižih delova mozga u cilju eliminacije prolazne hipoksije fetalnog nervnog sistema.Za procenu integriteta centralnog nervnog sistema fetusa upotrebom 4D ultrazvuka koristili smo Kurjakov antenatalni neurološki test – KANET.

KANET test kod trudnica sa gestacijskim dijabetes melitusom

Naša studija je obuhvatala 32 trudnice sa gestacijskim diabetes melitusom. U 19 (69,37%) od njih postojale su razlike jednog od ispitivanih parametara KANET skora koje su bile značajno različite i one su nađene za izolovanu retrofleksiju glave, izolovano treptanje oka, izraz lica, pokrete usana, izolovane pokrete ruke i za generalizovane pokrete. Za izolovane pokrete noge i za kranijalne suture razlike nisu bile značajne. KANET skor u ovoj grupi je bio od 8-11. ATNAT test je primenljiv za ovu grupu do dve godine starosti.

KANET test kod trudnica sa preterminskom prevremenom rupturom plodovih ovojaka

Naše ispitivanje je obuhvatilo 30 trudnicu sa preterminskom prevremenom rupturom plodovih ovojaka. Naši rezultati ukazuju da od 25-33 nedelje trudnoće dolazi do smanjenja pokreta glave i izraza lica fetusa.. KANET skor je bio od 6-13. Postoji i redukcija disajnih pokreta i refleksa hvatanja. Dolazi do promena u fetalnoj cerebralnoj cirkulaciji sa porastom protoka na kraju dijastole u a. cerebri medii.

KANET test kod trudnica sa postterminskom trudnoćom

Naše ispitivanje je obuhvatalo 11 trudnica sa postterminskom trudnoćom.Kod postterminskih trudnoća KANET skor je bio od 7-11, postoji redukcija fetalnih pokreta i velika incidenca fetalnih pokreta sličnih onim kod iritacije centralnog nervnog sistema.

Diskusija

Embrionalni i fetalni pokreti predstavljaju osnovnu fundamentalnu ekspresiju ranog neurološkog razvoja. Rani embrionalni razvoj karakteriše nepokretnost embriona (7). Prve spontane pokrete embriona u našem ispitivanju smo registrovali u 7,4 nedelje trudnoćese . Oni se sastoje od spore fleksije i ekstenzije trupa, a praćeni su pasivnim promenama položaja fetalnih ekstremiteta. Generalizovani pokreti celog tela se javljaju kasnije, u 9 nedelji trudnoće (8).U našem ispitivanju ispitivanju generalizovane pokrete smo registrovali u 8,3 nedelje trudnoće. Pokrete ruke prema glavi fetusa i pokrete rotacije glave fetusa smo registrovali u 10 .nedelji trudnoće. Otvaranje usta i disajne pokrete smo registrovali

u 10,5 nedelji trudnoće a pokrete gutanja u 12.nedelji trudnoće. Od 10 nedelje trudnoće raste broj i učestalost fetalnih pokreta (2). Kompleksni pokreti se pojavljuju u 10-12 nedelji trudnoće. U 11-12 nedelji trudnoće javljaju se izolovani pokreti ruku i nogu.U 14 nedelji trudnoće su češći i organizovaniji pokreti nego u 12 nedelji trudnoće (9). Razvoj vegetativnog nervnog sistema se evidentira u embrionalnoj srčanoj radnji u 5,5 nedelji trudnoće a potom i kroz evidenciju pokreta gutanja, štucanja, disajnih pokreta i dr. Glavna karakteristika druge polovine trudnoće je organizacija fetalnih pokreta. Poslednjih 10 nedelja trudnoće smanjuje se broj krupnih pokreta tela, a dolazi do porasta broja pokreta lica (10). Pokreti očiju se mogu pratiti u III trimestru. Oni se pojavljuju između 16-18 nedelje trudnoće u vidu pojedinačnih pokreta. U 22 nedelji trudnoće primećuje se otvaranje očiju a u 33 nedelji mogu se razlikovati brzi i spori pokreti očiju (11). Prepoznavanje prvih refleksa je mera neurološkog razvoja u drugom i trećem trimestru trudnoće od kojih su refleks hvatanja i Moro refleks dva najznačajnija. Palmarni refleks hvatanja pupčanika smo detektovali u preko 95% ispitivanih fetusa. Ovaj refleks je prisutan na rođenju i traje u prva 3 meseca života. Sumnjivo je ako ovaj refleks postoji i posle 3 meseca života, a nenormalno je ako se održava i posle 6 meseci. On je zavisan od motornog dela korteksa (12). Moro refleks se razvija u 9. nedelji trudnoće a potpuno je razvijen oko 34. nedelje trudnoće. Fetus pomera ruke napred i u stranu sa ekstenzijom podlaktica i šaka. On je prisutan na rođenju i perzistira 4-6 meseci. Njegovo odsustvo u prvih nekoliko meseci je nađeno kod teških cerebralnih oštećenja. Pokreti zevanja fetusa u našem ispitivanju u grupi trudnica sa 40+6 nedelja trudnoće su bili značajno učestaliji nego u grupi trudnica od 37-40 nedelje trudnoće, $p<0.05$. Pokreti zevanja nisu do sada kompletno objašnjeni. Ovi pokreti su pokrenuti aktivnošću nižih delova mozga u cilju eliminacije prolazne hipoksije fetalnog nervnog sistema. Procena fetalnog ponašanja za vreme različitih perioda gestacije mogla bi poslužiti za razlikovanje između normalnog i abnormalnog razvoja mozga (6). Zagrebačka grupa je 2008 godine napravila test za procenu integriteta fetalnog centralnog nervnog sistema upotrebom 4D ultrazvuka. To je Kurjakov antenatalni neurološki test - KANET. Ovaj test je standardizovan u Osaki u Japanu 2010 godine. KANET se izvodi u trećem trimestru trudnoće između 28 i 38 nedelje trudnoće. Ispitivanje ovim testom traje do 30 minuta . Normalni fetusi imaju KANET skor između 14-20, što predstavlja skor optimalnog neurološkog razvoja. Fetusi sa potencijalnim neurološkim abnormalnostima imaju skor od 5-13. Fetusi koji su neurološki abnormalni imaju prenatalni skor od 0-5 (13). U našem ispitivanju KANET testom kod trudnica sa gestacijskim dijabetes melitusom vrednosti KANET skora su bile od 8-11, u grupi trudnica sa preterminskkom prevremenom rupturom plodovih ovojaka KANET skor je bio od 6-13, a u grupi trudnica sa postterminskom trudnoćom vrednosti KANET skora su bile od 7-11. Za procenu neurološkog statusa novorođenčeta koristi se neonatalni neurološki test Amiel-Tison sa upotrebom 4D ultrazvuka, ATNAT-Amiel Tison Neurological Assessment at Term (14). Test se zasniva na saznanju o neurološkoj maturaciji delova centralnog nervnog sistema. Dva sistema kontrolišu motoriku fetusa i novorođenčeta. Donji sistem (produžena moždina i mali mozak) održava posturalnu kontrolu protiv sile teže i kontrolu mišića fleksora ekstremiteta. Klinički se procenjuje od 28 nedelje trudnoće. Gornji sistem (moždane hemisfere i bazalne ganglije) kontroliše donji sistem uz relaksaciju ekstremiteta. Klinički se procenjuje od 34 nedelje trudnoće (10). Ako su vrednosti testa granične ili abnormalne, onda se posmatarju veliki pokreti do 46 nedelje od menstruacije ili do pojave neurološkog ispada u prve dve godine života.

Zaključak

Ultrasonografske tehnike a posebno 4D ultrazvuk omogućuju praćenje fetalnog neurološkog razvoja i fetalnih ponašanja. Naša studija je pokazala da se nakon generalizovanih pokreta u I trimestru javljaju izolovani pokreti ekstremiteta, čija incidenca raste do 14. nedelje trudnoće. Prvi znak razvoja vegetativnog nervnog sistema je evidencija srčane radnje u 5,5 nedelji gestacije. Prvi motorni refleks je refleks hvatanja u 11,4 nedelji trudnoće, čija incidenca postepeno opada u II i III trimestru. Faze mira i aktivnosti su siklične u odnosu 1:2. Upotrebom 4D ultrazvuka i određivanjem vrednosti KANET skora može se proceniti integritet centralnog nervnog sistema fetusa.Vrednosti KANET skora u grupi trudnica sa gestacijskim dijabetesom, preterminskim prevremenim prsnućem plodovih ovojaka i postterminskom trudnoćom u našem ispitivanju ukazuju da su to fetusi sa potencijalnim neurološkim abnormalnostima.U perspektivi će poseban značaj imati istraživanja fetalne cerebralne cirkulacije i fetalnih facijalnih ekspresija u drugom i trećem trimestru trudnoće.

Napomena

Rad je usmeno izložen na mini simpozijumu Aktuelna dostignuća u savremenoj ginekologiji i akušerstvu na 44. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 10.12.2015. godine.

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SURGICAL TREATMENT OF ANORECTAL ANOMALIES IN CHILDREN: EXPERIENCE WITH 224 PATIENTS

HIRURŠKO LEČENJE ANOREKTALNIH ANOMALIJA KOD DECE: ISKUSTVO NA 224 PACIJENTA

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Summary

Anorectal anomalies (ARA) are congenital malformations that are represented by a wide spectrum of defects. This report describes the authors' experience and results of surgical treatment of ARA. The aim of this study was to analyse the functional outcome in patients following standardized surgical treatment of ARA.

A total of 224 patients (115 girls and 109 boys) were treated from 1988 to 2015 and the data were analysed. All patients underwent a follow up by the author. Postoperative anorectal function was evaluated based on the ability to have voluntary bowel movement, soiling and constipation. In cases of faecal incontinence bowel management program was applied.

In our series of 224 operated patients 52 (24%) had faecal incontinence. Bowel management program was implemented in those patients, with a success rate of 90,6 % immediately after the treatment started in hospital, with a decrease to 83,7 % at home. In puberty success rate increased to 95%. Malone's antegrade enema procedure (ACE procedure) was done in 9 patients. It was successful in 100% of cases in the first year, with complication rate of 44% afterwards (conduit stenosis and leakage).

Bowel management program offers significant benefits to children with faecal incontinence after surgical treatment of ARA. The ACE procedure can be implemented in patients after successful bowel management. Although patients are satisfied with ACE procedure, complications are very common.

Keywords: anorectal anomalies, outcome, bowel management, ACE procedure.

Sažetak

Anorektalne anomalije (ARA) su kongenitalne malformacije koje čine širok spektar poremećaja. Ovaj rad opisuje autorovo iskustvo i rezultate hirurškog lečenja ARA. Cilj ovog ispitivanja je bila analiza funkcionalnog ishoda u pacijenata nakon standardnog hirurškog lečenja ARA.

Od 1988. do 2015. je ukupno lečeno 224 pacijenata (115 devojčica i 109 dečaka) i njihovi podaci su analizirani. Svi pacijenti su praćeni od strane autora. Postoperativno je praćena anorektalna funkcija bazirana na sposobnosti voljnog pražnjenja creva, prljanja veša i opstipacije. U slučajevima fekalne inkontinencije primenjen je program tretmana creva (bowel management).

U našoj seriji 224 operisana pacijenta 52 (24%) je bilo fekalno inkontinentno. Program tretmana creva je bio primenjen kod tih pacijenata, sa uspešnošću od 90,6% neposredno nakon što je lečenje završeno u bolnici, a uspešnosti kod kuće se smanjila na 83,7%. U vreme puberteta uspešnost tretmana creva je porasla na 95%. Maloneova procedura antegradne klizme (ACE procedura) je primenjena u 9 pacijenata. Ona je bila uspešna 100% u prvoj godini, sa komplikacijama u 44% slučajeva (stenoza i kvašenje konduita).

Program tretmana creva nudi značajni boljitak deci sa fekalnom inkontinencijom nakon hirurškog lečenja ARA. Maloneova ACE procedura se može primeniti kod pacijenta nakon uspešnog programa tretmana creva. Premda su pacijenti sa ACE procedurom zadovoljni, procenat komplikacija je velik.

Ključne reči: anorektalna anomalija, ishod lečenja, tretman creva (bowel management), ACE procedura

Uvod

Anorektalne anomalije (ARA) predstavljaju širok spektar kongenitalnih poremećaja u razvoju završnog dela digestivnog trakta, veoma često udružene sa regionalnim anomalijama urogenitalnog trakta i sakruma, kao i drugim urođenim anomalijama. Klasifikacija ovih anomalija prema lokaciji i visini fistule između rektuma i urogenitalnog trakta kao i savremen pristup u operativnom lečenju počinje osamdesetih godina prošlog veka primenom posterio-sagitalnog pristupa (1). Od 1982. ova klasifikacija i operativna tehnika sa kojom je jasno vidljiva patološka anatomija anomalije omogućava preciznu operativnu rekonstrukciju. Posterio-sagitalni pristup je prihvaćena u svetu kao standardan način lečenja. Na našoj klinici ovaj način operativnog lečenje se primenjuje od 1988. godine.

I pored korektne anatomske rekonstrukcije anomalije, fekalna inkontinencija i disfunkcija analnog sfinktera su često prisutne u ovih pacijenata i utiču na kvalitet života. Fekalna inkontinencija prati oko 25% pacijenata nakon lečenja anorektalnih anomalija (2). Deca sa fekalnom inkontinencijom imaju loš kvalitet života i kada postanu svesvni svog nedostatka mnogo pate. Osim inkontinencije, opstipacija je izuzetno čest funkcionalni poremećaj koji prati pacijente sa anorektalnim anomalijama u postoperativnom toku. Ukoliko se ne dijagnostikuje i ne leči adekvatno predstavlja ozbiljan funkcionalni problem pacijentu. Morbiditet koji proističe iz

loše lečene opstipacije kod pacijenata sa ARA uključuje opstrukciju creva fekalnim masama, sekundarni megakolon i pseudoinkontinenciju (3,4). Tretman creva (bowel management) je konzervativan način lečenja fekalne inkontinencije koji se uspešno sprovodi i poboljšava kvalitet života pacijenata (5,6).

Cilj rada

Analiza rezultata operativnog lečenja u svetlu postizanja fekalne i urinarne kontinencije i primena tretmana creva u poboljšanju kvaliteta života.

Materijal i metode

Retrospektivnim uvidom u kliničku i radiografsku dokumentaciju 224 pacijenta operisanih zbog anorektalnih anomalija u periodu 1988-2015 godine analizirane su operativne procedure, komplikacije i ishod lečenja. Fekalna i urinarna inkontinecija je evaluirana kod pacijenata starijih od 3 godine. Kriterijum za fekalnu kontinenciju je bila sposobnost da se dete spontano i kontrolisano prazni bez pomoći supozitorija ili klizme. Evaluacija urinarne kontinencije se zasnivala na sposobnosti deteta da spontano i kontrolisano u potpunosti prazni bešiku. Dva pacijenta koja su umrla pre, a dva nakon operacije otvaranja kolostome u periodu između 1988-1998, sa udruženim kompleksnim anomalijama nisu uzeta u razmatranje u ovoj studiji. U slučajevima fekalne kontinencije primenjen je tretman creva i praćen njegov ishod. U postoperativnom toku se pratila fekalna kontinencija i u slučajevima postojanja inkontinencije pacijenti uzrasta starijeg od 3 godine su uključeni u program tretmana creva. U zavisnosti od tipa motiliteta kolona, da li je motilitet usporen (opstipacija) ili hiperaktivan (dijareja) prilagođavao se tretman creva. Tretman creva se sastojao od dnevnih klizmi sa fiziološkim rastvorom ili hipertonim slanim rastvorom, uz dodatak glicerina ili parafina. Količina klizme i njena koncentracija je određivana putem pokušaja i greške. Klinički odgovor, tj. stepen pražnjena crvea je praćen radiografski kao i na osnovu rezultata. Dobar rezultat je smatran ako dete nakon klizme ima obilno pražnjenje creva i naredna 24h ne prlja veš. U slučaju da je kolon hiperaktivan uz konstipativnu dijetu je dodavan loperamid. Deca su hospitalizovana 7 dana uz obuku majke da sprovode tretman creva. Nakon otpusta majke su vodile dnevnik o količini i sastavu date klizme i svakodnevnom rezultatu, tj. prljanju ili ne prljanju veša.

Rezultati

U našoj seriji lečili smo ukupno 224 pacijenta, od kojih 115 devojčica, od čega 26 sa kloakalnom anomalijom. U grupi dečaka lečeno je 109 pacijenata, od kojih 3 sa rektovezikalnom fistulom. Svi pacijenti su operisani posterio-sagitalnim, anteriosagitalnim ili transrektalnim pristupom (posterior kloake). U slučajevima rektovezikalne fistule kao i potrebe „vaginalnog switch-a“ pristupalo se kombinovano posterio-sagitalnim pristupom i laparotomijom.

Od 26 pacijenata sa kolakalnom anomalijom u 6 je postojala varijacija pod nazivom posterior kloaka. Sve devojčice sa posterior kloakom su imale akcesornu uretru, kod 4 je pristupljeno transanorektalnim pristupom, a kod 2 anterosagitalnim. Pet pacijenata sa klasičnom kloakom je zahtevalo laparotomiju, u tri slučaja je rađen „vaginal switch“, a u 2 zamena vagine sa ilealnim konduitom. U 19 pacijenata sa kloakom je rađena totalna urogenitalna mobilizacija. Kloakalna anomalija je bila udružena sa hidrokolposom u 8 pacijenata, a u 7 je dijagnoza postavljena prenatalno. Kod svih novorođenčadi sa hidrokolposom i prenatalno postavljenom dijagnozom bile su prisutne duple Milerove strukture. Hidrokolpos je bio praćen udru\enom megaureterohidronefrozom u 8 novorođenih devojčica sa kloakom. Svim pacijentima sa hidrokolposom je rađena ili vaginalna drenaža (2) ili vezikostoma (6).

Reoperacija je rađena kod 1 pacijenta zbog pogrešno lociranog anusa. Vaginalna striktura je operisana u 2 devojčice nakon operacije kloakalne anomalije. Jedna rekurentna rektovaginalna fistulu nakon operacije atrezije anusa sa rektovestibularnom fistulom je zahtevala reoperaciju. Analna stenoza se javila u devojčice koja je razvila ulcerozni kolitis refrakteran na konzervativnu terapiju i za sada ima otvorenu ileostomu. U 13 pacijenata su rađene manje korekcije zbog prolapsa rektalne sluznice.

U našoj seriji od 224 operisana pacijent 52 (24%) su bila fekalno inkontinentni. Lečenje je bilo operativno u 9 pacijenata kod kojih je učinjena Maloneova ACE procedura („antegrade continence enema”), a kod ostalih 43 je sproveden tretman creva („bowel management“). Operativno lečenje je sprovedeno kod pacijenata kod kojih je prethodno uspešno sprovođen „bowel managemet“. Tretman creva je uvek uspostavljen u bolničkim uslovima, pri čemu se odredjivala količina i sastav klizme (fiziološki rastvor, hipertoni slani rastvor, dodatak sapunice, glicerina, parafina) i dijeta, čime se postizalo da pacijent tokom naredna 24h bude čist i u svom vešu bez pelena. Praćenje pražnjenja creva je vršeno nativnim radiografskim snimcima. Uspešnim se smatralo lečenje koje je omogućilo da pacijent 24h nakon tretmana bude čist, tj. ne prlja veš. Majke su obučene za tretman creva. Pacijenti su periodično kontrolisani, a u međuvremenu su majke vodile dnevnik u koji su beležile neophodne podatke o načinu pražnjenja creva i prljanju veša. Inicijalno uspeh je postignut primenom tretmana creva u 39 (90,6%) konzervativno lečenih pacijenta. Nakon odlaska kući i promene uslova u odnosu na bolničke,

uspešnost je u prva 3 meseca nakon započinjanja konzervativne terapije smanjena na 83,7% (36 pacijenata). Evaluacija uspešnosti lečenja nakon 1 godine je bila 93% (40 pacijenata). Pacijenti koji su ušli u pubertet (stariji od 13. godina), su dostigli uspešnost lečenja od 95%. Operativno lečeni pacijenti ACE procedurom su imali uspešnost 100% u prvoj godini lečenja. Komplikacije u vidu stenoze ili kvašenja oko stome su se javile u 4 (44%) pacijenta. Stenoza je rešena dilatacijom, a kvašenje oko stome endoskopskim ubrizgavanjem kopolimera dekstranomer hijaluronične kiseline (Deflux paste).

Urinarna inkontinencija se lečila čistom intermitentnom kateterizacijom mokraćne bešike u 9 pacijenata, od toga transuretralno u 7 (sve devojčice), a kroz konduit po Mitrofanoffu u 2 slučaja.

Diskusija

I pored velikog napretka u operativnom lečenju kongenitalnih anorektalnih anomalija u poslednjih 30 godina, značajan procenat dece ima dugotrajne probleme sa fekalnom inkontinencijom, što prouzrokuje psihološke i socijalne probleme. Osim fekalne inkontinencije, koja se javlja u oko 25% do 30% pacijenata operisanih zbog anorektalnih anomalija, još oko 30% ovih pacijenata imaju druge funkcionalne poremećaje defekacije kao što su opstipacija, povremo prljanje veša i fekalna inkontinencija tokom perioda dijareje. Opstipacija je najznačajnija postoperativna funkcionalna komplikacija i javlja se u rasponu od 10% do 73%. Opstipacija je povremeno praćena prelivanjem fekalnog sadržaja što dovodi do pseudoinkontinencije i prljanja veša.

Lečenje fekalne inkontinencije u dece operisane zbog anorektalnih anomalija podrazmeva razlikovanje dve grupe poremećaja (7). Prvu grupu pacijenata čine oni sa istinskom fekalnom inkontinencijom, koji nemaju voljno pražnjenje creva jer su rođeni sa tipom anomalije koja ima lošu prognozu (rektovezikalna fistula, kloaka sa zajedničkim kanalom dužim od 3cm, „tethered cord“, agenezija više od 2 sakralna pršljena). Drugu grupu pacijenata čine oni koji su rođeni sa anorekatalnom anomalijom koja ima prognostički dobru funkciju, ali izraženu opstipaciju koja je loše lečena, te su razvili pseudoinkontinenciju. Ova druga grupa nakon pražnjenja fekalnih masa i ispravne doze laksativa ima voljno pražnjenje develog creva i prestaje da prlja veš.

Tretman creva (bowel management), koji je započet pre 30 godina od strane Alberta Pene i Marka Levitta (8) je lako sprovodljiv u kućnim uslovima od strane roditelja, nije skup i ima uspešnost u 95% pacijenata (9). Naši rezultati su vrlo slični literaturi. Inicijalni uspeh tokom bolničke primene tretmana creva na kontrolu pražnjena je postignut kod 90,6% pacijenata. I pored nešto manje uspešnosti po odlasku u kućne uslove (83,7%), do porasta u kontrolisanom pražnjenju dolazi već nakon prve godine primene ovog sistema, jer se porodica obuči da prati promene u pražnjenju creva i izvrši sama potrebne korekcije. Nakon puberteta dolazi do poboljšanja fekalne kontinencije i u slučajevima visokih anomalija što se tumači nestankom opstipacije koja je glavni uzrok funkcionalnih problema u ranom uzrastu (10). Za razliku od ovih rezultata, ispitivanje funkcionalnih poremećaja i dugotrajnog kvaliteta života pacijenata sa visokim anorektalnim anomalijama od strane Hashisha i saradnika (11) je pokazalo da se obrazac pražnjena creva pogoršava sa uzrastom. Međutim ovi pacijenti nisu bili u programu tretmana creva. U našoj seriji primene tretmana creva imali smo uspešnost od 95% nakon puberteta, što je posledica mnogo manje izražene opstipacije, ali i motivisanosti samog pacijenta da se pridržava programa tretmana creva. U nastojanju da se pacijenti u programu tretmana creva osamostale u procesu davanja klizmi, Malone je 1990. promenom smera davanja klizme, antegradnim putem, (ACE procedura) kroz apendix, omogućio efikasnije pražnjenje creva (12). Ova metoda se od tada uspešno primenjuje u lečenju fekalne inkontinencije različite etiologije (13). U slučajevima kada uz fekalnu postoji i urinarna inkontinencija primenjuju se operativne tehnike po Mitrofanoffu (14) i Montiju (15) za obezbeđivanje antegradnog puta čiste intermitentne kateterizacije mokraćne bešike. Procedure se razlikuju prema tkivu koje se koristi za konduit preko koga se vrši kateterizacija bešike. U slučaju procedure po Mitrofanoffu konduit je apendiks, a po Montiju segment tankog creva. Bez obzira da li se koristi samo ACE procedura ili u kombinaciji sa konduitom za kateterizaciju bešike (procedura po Mitrofanoffu ili Montiju) komplikacije su česte (57%). Najčešća komplikacija je stenoza stome (41%), kvašenje u predelu stome, perforacija cekuma zbog otežane kateterizacije. U našoj seriji smo imali ukupno 44% komplikacija, ali je mali broj pacijenata lečen na ovaj način.

Zaključak

Anorektalne anomalije još uvek predstavljaju najsloženije kongenitalne anomalije gastrointestinalnog trakta s obzirom da zahvataju više sistema. Za lečenje komplikovanih visokih anomalija potreban je iskusan i obučen tim. S aspekta funkcionalnog rezultata lečenja najsloženije anomalije i dalje imaju lošu prognozu u smislu fekalne i urinarne kontinencije. Primenom sistema tretmana creva može se postići kontrolisano pražnjenje i socijalna integracija između 90-95% pacijenata. Urinarna kontinencija je mnogo ređe ugrožena, ali ukoliko postoji neminovna je intermitentna čista kateterizacija bešike.

Program tretmana creva nudi značajni boljitak deci sa fekalnom inkontinencijom nakon hirurškog lečenja ARA. Maloneova ACE procedura se može primeniti kod pacijenta nakon uspešnog programa tretmana creva. Premda su pacijenti sa ACE procedurom zadovoljni, procenat komplikacija je velik.

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LIFESTYLE CHANGES AND MEDICAL THERAPY IN SLOWING THE GROWTH OF SMALL ABDOMINAL AORTIC ANEURYSMS

PROMENE NAČINA ŽIVOTA I MEDIKAMENTNA TERAPIJA U USPORAVANJU RASTA MALIH ANEURIZMI ABDOMINALNE AORTE

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Summary

The goal of our review was to evaluate the impact of lifestyle changes and medical therapy in slowing the growth of small abdominal aortic aneurysms (AAA), as well as to introduce current ideas for future treatment. No viable evidence was found that medical therapy can slow the growth of small AAAs. The beneficial role of propranolol, angiotensin-converting enzyme inhibitors and doxycycline in reducing the growth rate of AAA was ruled out by randomized controlled studies, whereas the efficiency of statins, macrolides and anti-platelet therapy remains controversial. On the other hand, smoking cessation is the only established lifestyle change that was effective in impeding the AAA expansion. Also, there are a considerable number of novel therapeutic strategies related to the problem, which still need to be evaluated in clinical trials, including administration of Cyclosporine A, gene therapy and mesenchymal stem cell treatment.

Keywords: abdominal aortic aneurysm, medical therapy, lifestyle changes, growth.

Sažetak

Cilj našeg rada je bio da ispitamo uticaj promena načina života i medikamentne terapije na usporavanje rasta aneurizmi abdominalne aorte (AAA) i da ukažemo na aktuelne ideje za budući tretman. Nismo pronašli zadovoljavajuće dokaze da medikamentna terapije može da uspori rast malih AAA. Randomizovane kontrolisane studije su opovrgle povoljnu uloga propranolola, inhibitora angiotenzin-konvertujućeg enzima i doksiciklina u smanjenju rasta AAA, dok je efikasnost statina, makrolida i anti-trombocitnih lekova i dalje sporna. Sa druge strane, prestanak pušenja je jedina promena u načinu života koja se pokazala efikasnom u usporavanju rasta AAA. Takodje, značajnom broju novih terapeutskih strategija za usporavanje rasta AAA predstoje klinička ispitivanja, uključujući primenu ciklosporina A, genetsku terapiju i lokalnu primenu mezenhimalnih matičnih ćelija.

Ključne reči: aneurizma abdominalne aorte, medikamentna terapija, način života, rast.

Introduction

Abdominal aortic aneurysm (AAA) is a disease with vague or absent symptoms, which can have catastrophic consequences. Its prevalence in elderly population ranges from 4.0% to 7.2%, with a strong male preponderance (9, 12, 30). In a population-based study the overall mortality associated with AAA rupture was around 80%, with the majority of deaths occurring outside hospital (10). It is established that AAAs with a diameter ≥5.5 cm have a high incidence of rupture, and thus should be treated either with open surgery or with endovascular aneurysm repair (EVAR) (19, 35).

Due to the increasing number of screening programs, there is a growing population of patients aged 65-80 with a small AAA of 3.0 to 5.5 cm in diameter, which are considered safe for observation (11). As aneurysms grow over time, for instance, a 4.5 cm aneurysm would take 2.3 years on average to reach 5.5 cm in diameter, there is a need for non-invasive therapy that would suspend the growth of small AAAs (39).

There is an abundance of preclinical studies using different approaches to impede the aneurysmal growth in animal models (15, 47). In contrast, clinical studies on the subject are scant and their results vary considerably (4, 21, 26, 38). The goal of our review was to evaluate the impact of lifestyle changes and medical therapy in slowing the growth of small AAAs, and to introduce current ideas for future treatment.

The effectiveness of lifestyle changes

Smoking is the most important modifiable risk factor associated with development and expansion of AAA. A recent study including 567 patients from the Aneurysm Detection and Management (ADAM) trial showed that current smoking was a significant risk factor for expansion rate of AAA, aside from the elevated diastolic blood pressure (5). Also, smoking was the only risk factor The United Kingdom Small Aneurysmal Trial (UKSAT) linked with the increased growth rate of AAAs (8). Furthermore, in a systematic review by Lederle et al,

current smokers had a higher relative risk of abdominal aorta-related events than of coronary artery disease and cerebrovascular disease. Therefore, there is no doubt that the smoking cessation should be a standard course of action in patients with small AAAs. Several pharmaceutical agents were developed to help in this effort, varenicline being the most efficient one (20).

All the major guidelines recommend moderate physical activity for prevention and treatment of cardiovascular diseases (23, 46). Additionally, patients with prolonged sedentary lifestyle are more likely to develop AAA (49, 52). Several small studies have shown benefits of physical exercise therapy in terms of cardiopulmonary fitness of patients, but without any effects on AAA growth (28, 37, 44). There is an evident need for larger studies regarding this subject, however patient compliance could present as a major obstacle.

The impact of cardiovascular risk reducing drugs

Early reports gave incentive to evaluate the effect of beta blockers on aneurysmal expansion process (29). Wilmink et al. used data from two major cohorts in a case control study to find no significant evidence of beta blockers influence on AAA growth rate (50). In Propranolol Aneurysm Trial Investigators (PATI) study 548 patients with small AAAs were randomized to either propranolol or placebo control group (40). Even though patients receiving propranolol were less likely to undergo elective aneurysmal repair, there was no significant difference in growth rates of AAA between the groups. Patients with slow-growing AAAs and patients with previously prescribed beta blockers were not included in this trial. The only two randomized control trials (RCT) on the subject showed that propranolol was poorly tolerated in standard dosage, (31, 40) thus leaving the possibility of other beta blockers being more effective in reducing the AAA growth.

Two large retrospective studies concluded that even though angiotensin converting enzyme (ACE) inhibitors reduce the inflammation in the aneurysmatic tissue, they do not affect the aneurysmal growth rate (27, 45). On the other hand, in a prospective study of 1701 participants in UKSAT trial, the use of ACE inhibitors was linked with a significant increase in AAA growth rate (43). In addition, another large case control study found that ACE inhibitor use decreases aortic wall stiffness and increases collagen turnover, further suggesting the negative role of ACE inhibitors in aneurysmatic disease of abdominal aorta (50).

No association was found between other classes of antihypertensive drugs and expansion rate of AAA (5, 50).

Apart from their original effect of reducing cholesterol levels in blood, statins also decrease the activity of proteolytic enzymes in the aneurysmal tissue (51). To this day the role of statins in slowing the aneurysmal growth has been controversial (18). A meta-analysis by Twine et al. found insufficient evidence to confirm the restraining effect of statins on AAA growth (48). However, four high-quality studies from this review reported no significant difference in aneurysmal growth between the statin and the control group. Another more recent meta-analysis of 11 observational comparative studies showed that statin therapy was efficient in decreasing the growth rate of AAAs, especially those with the baseline diameter >3.6 cm. Nevertheless, there are still no RCTs on the subject to resolve the dilemma.

Anti-platelet therapy is associated with good outcomes in patients with cardiovascular disease (2). However, evidence on the influence of antiplatelet therapy on aneurysmal growth is limited. A case control study, conducted on 167 patients, reported that the growth rate of AAAs with a diameter of 4.0 to 4.9 mm is reduced in patients on anti-platelet therapy (32). On the other hand, analyses based on the data from large screening studies showed that there was no link between antiplatelet drugs and AAA growth rate (5, 43). It is still unclear if standard antithrombotic doses of aspirin are sufficient for any notable effects on AAA expansion.

The role of antibiotics

Tetracyclines are broad-spectrum antibiotics, which also inhibit the production of proteolytic enzymes and reduce the level of inflammation in human tissue (41). Several small RCTs provided promising results of short-term doxycycline treatment in slowing AAA growth (3, 36). In contrast, a later multicentre RCT reported that patients using doxycycline had an increased expansion rate of AAA over time, implying the negative effect of tetracycline therapy on patients with AAA (34).

Early reports, which suggested that chlamydial infection had a considerable role in formation of AAA, led to a hypothesis for macrolides efficacy in treatment of small AAAs (24, 25). Two small-sample RCTs associated roxithromicyn administration with a decrease in AAA growth. A large RCT, including 213 patients followed-up for a minimum of 18 months, showed no significant difference in AAA growth rates between patients on azithromycin therapy and the control group.

Future therapeutic strategies

Over the past decade a considerable progress has been made in understanding cellular mechanisms behind aortic aneurysm formation and its development. It has

been established that depletion of vascular smooth muscle cells and degradation of the extracellular matrix, both induced by inflammation, lead to the weakening of the aortic wall and its tendency to rupture (22). Thus began the search for therapeutic options to suspend and reverse these processes.

In their earliest two papers, Allair et al. demonstrated the role of transforming growth factor β (TGF-β) in stabilizing predeveloped aneurysms in an aortic xenograft model by seeding genetically-modified vascular smooth muscle cells (1, 33). In their further research they successfully used gene implementation therapy via adenovirus vectors to promote TGF-β activity in two animal models and human AAA explants (13). Their latest work proposed a short-course administration of Cyclosporin A to increase TGF-β levels in aortic tissue, thereby overcoming the disadvantages of gene and cell-implementation therapies (14). Additionally, they found that a 7-day course of Cyclosporin A had long-term effectiveness in experimental models, suggesting that TGF-B might be a self-promoting factor in abdominal aortic tissue.

A wide variety of genes has been associated with the formation of AAA, however most of these connections seem to be overestimated (7). On the other hand, there is an increasing interest in using non-coding RNAs for treatment of small AAAs, as their role in post-transcriptional processes becomes evident (16, 17).

Adventitial implantation of mesenchymal stem cells showed some success in impeding the process of AAA growth in animal models (6, 42). Although there are no human studies on this matter, focused delivery of stem cells to regenerate the medial tissue of the abdominal aorta is a promising option for the future.

Conclusion

Our review found no viable evidence that medical therapy can slow the growth of small AAAs. The beneficial role of propranolol, ACE inhibitors and doxycycline in reducing the growth rate of AAA was ruled out by RCTs, whereas the efficiency of statins, macrolides and anti-platelet therapy remains controversial. Smoking cessation is the only established lifestyle change that was undeniably effective in impeding the AAA expansion. There is a considerable number of novel therapeutic strategies related to the problem, which still need to be evaluated in clinical trials, including administration of Cyclosporine A, gene therapy and mesenchymal stem cell treatment.

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RIVAROXABAN VERSUS DABIGATRAN: A NEW ERA IN VENOUS THROMBOEMBOLISM TREATMENT

RIVAROKSABAN NASPRAM DABIGATRANA: NOVA ERA U TRETMANU VENSKOG TROMBOEMBOLIZMA

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Summary

Considering the frequency of deep vein thrombosis and pulmonary embolism, the therapy of these two conditions takes an important place in vascular surgery. Among numerous therapeutic options, new oral anticoagulants, such as rivaroxaban or dabigatran, represent a great improvement in the treatment of venous thromboembolism.

Searching MEDLINE base until December 1, 2015 using MESH term "Rivaroxaban versus Dabigatran in VTE", we found 7 studies investigating the usage of new oral anticoagulants in venous thromboembolism treatment. The total of 18,841 patients was enrolled. No head–to–head studies were found.

Benefits such as lower therapy price, oral use and greater comfort for patients and health providers place new oral anticoagulants to the frontline of venous thromboembolism treatment.

However, we need head to-head studies to have a clear picture of these two drugs.

Keywords: Rivaroxaban, Dabigatran, new oral anticoagulants, venous thromboembolism, deep vein thrombosis, pulmonary embolism.

Sažetak

Uzimajući u obzir incidenciju tromboze dubokih vena i plućne embolije, terapija ovih stanja zauzima značajno mesto u vaskularnoj hirurgiji. Postoji više izbora lečenja, a novi oralni antikoagulansi, kao što su rivaroksaban i dabigatran, predstavljaju veliki pomak u terapiji venskih tromboembolijskih stanja.

Pretražujući bazu podataka MEDLINE koristeći MESH izraz "Rivaroxaban versus Dabigatran in VTE" pronađeno je 7 studija sa ukupno 18841 ispitanikom. Nije pronađena nijedna studija koja direktno upoređuje upotrebu rivaroksabana i dabigatrana u terapiji venskih tromboembolijskih stanja.

Oralna upotreba, niža cena lečenja kao i veći komfor za pacijente i lekare prednosti su novih oralnih antikoagulanasa u terapiji venskih tromboembolijskih stanja.

Studije koje direktno uporedjuju Rivaroxaban i Dabigatran su neophodne radi boljeg razumevanja efekata ova dva leka.

Ključne reči: Rivaroksaban, Dabigatran, novi oralni antikoagulansi, venski tromboembolizam, dubinska venska tromboza, embolija pluća

Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE) are not that rare in vascular pathology. DVT occurs in 1 per 1000 adults each year, increasing to 7 per 1000 yearly in population aged ≥ 75 (1-3). Incidence of PE amounts to 49 per 100,000 persons (4). It is an expensive condition to treat, costing between $7.5 to $39 billion per year in the USA alone (5). Postthrombotic syndrome (PTS), which occurs in 20-60% of patients with prior DVT, increases the cost of treatment up to 75% (6). A study of Tagalakis et al. evaluated short and long-term mortality after 67,354 definite and 35,123 probable cases of VTE. They found that 30-day and one year case fatality rates were 10.6 and 23.0%, respectively (7).

In recent years, several new oral anticoagulants (NOACs) have been developed for the treatment of VTE, such as direct factor Xa inhibitor rivaroxaban (Xarelto®, Bayer AG, Leverkusen, Germany) (8) and direct thrombin inhibitor dabigatran (Pradaxa®, Boehringer Ingelheim, Ingelheim, Germany) (9). Dabigatran has just recently been approved for treating acute VTE and it was approved for prevention of recurrent events in early 2014. Rivaroxaban was approved for this indication by the Food and Drug Administration (FDA) in 2012 (10).

NOACs have opened a new chapter in VTE treatment, aiming at succeeding vitamin K antagonists (VKA). Comparison of NOACs and warfarin are shown in Table 1 (11, 12).

This review aims at summarizing the literature and previous studies of rivaroxaban and dabigatran in the treatment of VTE.

Table 1. Pharmacological characteristics of Rivaroxaban and Dabigatran in comparison with Warfarin

	Rivaroxaban	Dabigatran	Warfarin
Mechanism of action	Direct factor Xa inhibition	Direct thrombin inhibition	Inhibition of vitamin K epoxide-reductase
Molecular weight (Da)	436	628	≈ 1000
Bioavailability	80-100% with food	6-7%	>60%
Half-life	7-13 h	9-17 h	36-42 h
Dosing	Fixed, once daily	Fixed, once-twice daily	INR adjusted variable dosing
Protein binding (%)	92-95	33-35	≈99
Elimination	67% renal (half as an inactive form)	80% renal	Hepatic, primarily via CYP2C9
Reversal strategy	None	None	Vitamin K
Monitoring test	Not required routinely. Anti-Xa assay, PT with Neoplastin	Not required routinely. Diluted thrombin time	INR

Abbreviations: CYP, cytohrome P450; INR, international normalized ratio; PT – prothrombin time; Xa, activated Factor X.

Methods

We pre-specified the objectives and methods of this systematic review. Key points of interest were studies that compared the usage of rivaroxaban and dabigatran in treating acute and chronic DVT and PE. Studies were identified by scanning reference lists of other review articles and by searching MEDLINE base using PUBMED until December 1, 2015. We used MESH term "Rivaroxaban versus Dabigatran in VTE". Only full – text articles were included.

Results

The results of our search included 7 studies: 4 studies in acute VTE and 3 studies in chronic VTE treatment. Four studies investigated the usage of dabigatran (2 studies in acute and 2 studies in chronic VTE) while the usage of rivaroxaban was shown in 3 studies (2 studies in acute and one study in chronic VTE treatment). No head–to–head studies were found. 18,841 patients in total were enrolled. Across trials 55 – 61% of patients were males, the average age was 55 - 58 (11) (Table 2).

All the trials were double blinded, except EINSTEIN-DVT and EINSTEIN-PE. AThe assessment methods of recurrent VTE were consistent across studies (13-17). DVT diagnosis was established by venography or compression ultrasonography (CUS) of leg veins. Non-fatal PE was diagnosed using ventilation-perfusion lung scanning, angiography or spiral computed tomography of pulmonary arteries. Diagnosis of fatal PE was based on autopsy findings or death for which PE could not be excluded.

Bleeding definition criteria differed between trials (18, 19). Major bleeding was defined as symptomatic (dabigatran trials) or overt (rivaroxaban trials). Episodes of bleeding that did not match major bleeding criteria, but still needed medical observation, were defined as clinically relevant non-major (CRNM) bleeding. RECOVER I and II trials defined CRNM bleeding as one requiring hospitalization and/or surgery, and transfusion of <2 U of whole blood or red blood cells (10).

Trials with dabigatran considered the presence of symptomatic proximal DVT (defined as occurring in popliteal vein and above) with or without PE. Patients included in RE-MEDY or RE-SONATE trials had completed at least 3 months of treatment with warfarin or dabigatran (10). EINSTEIN PE trial included patients with symptomatic PE, with/without DVT, while EINSTEIN DVT trial required symptomatic proximal DVT without PE. EINSTEIN–Extension trial evaluated the long-term use of rivaroxaban for secondary prevention of VTE. Only EINSTEIN trials allowed concomitant use of dual antiplatelet therapy.

Exclusion criteria were similar across the studies: life expectancy < 3 months (EINSTEIN DVT, -PE) or < 6 months (RE-COVER I, II); creatinine clearance (CrCl) ≤ 30 mL/min and pregnancy as well.

Heparin lead-in was used in RE-COVER, while in EINSTEIN trials experimental group was taking only rivaroxaban. Treatment durations ranged from 3 to12 months in acute VTE treatment and 6 to 18 months in the extended therapy of VTE.

Placebo controlled studies were superiority trials (NOACs had better outcome than placebo), while other studies used non-inferiority approach (NOACs weren't inferior to drugs used in control groups). In trials with placebo-controlled groups patients were recruited if there was clinical doubt of continuation or cessation of anticoagulant therapy.

Table 2. Clinical trials with NOACs in VTE treatment

Study (NOAC)	N (patients)	Age (yrs)	Male sex (%)	Design	Experimental treatment	Control treatment
Acute treatment						
RE-COVER I[13] (Dabigatran)	2,564	55	58	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
RE-COVER II[14] (Dabigatran)	2,589	55	61	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
EINSTEIN DVT[15] (Rivaroxaban)	3,449	56	57	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
EINSTEIN PE[16] (Rivaroxaban)	4,833	58	53	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)
Extended treatment						
RE-MEDY[17] (Dabigatran)	2,866	55	61	DBRCNI	DAB 150 mg BID	Warfarin dose-adjusted (INR: 2.0–3.0)
RE-SONATE[17] (Dabigatran)	1,343	56	55	DBRCS	DAB 150 mg BID	Placebo
EINSTEIN-EXTENSION[15] (Rivaroxaban)	1,197	58	58	DBRCS	RIV 20 mg OD	Placebo

Abbreviations: BID, twice-daily; DAB, dabigatran; DBRCNI, double-blind randomized controlled non-inferiority trial; DBRCS, double-blind randomized controlled superiority trial; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; INR, International Normalized Ratio; N, total patients in the trial; NOAC, new oral anticoagulant; OD, once-daily; OLRCNI, open-label randomized controlled non-inferiority trial; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etexilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; RIV, rivaroxaban; VTE, venous thromboembolism; yrs, years.

Discussion

Acute VTE treatment trials showed no difference in recurrent, symptomatic VTE between two groups. In the active-control RE-MEDY trial, dabigatran demonstrated non-inferiority compared with warfarin regarding to recurrence of VTE (10). RE-SONATE trial, showed a 92 % reduction in the recurrent VTE, representing superiority of dabigatran over placebo (10). The incidence of recurrent, symptomatic VTE in EINSTEIN EXT trial was reduced by 82 % with the use of rivaroxaban (15). Death incidence related to VTE didn't differ significantly between trials (10, 15).

Bleeding complications were considerably reduced with the use of dabigatran in RE-COVER trials, as well as in RE-MEDY trial. While incidence of major bleeding was not notably increased with the use of dabigatran in RE-SONATE trial, there was a significant increase of other bleeding complications (10).

EINSTEIN-PE study showed reduced incidence of major bleeding in patients taking rivaroxaban. There was no difference of bleeding complications between groups in EINSTEIN-DVT trial. While the incidence of major bleeding in EINSTEIN-EXT trial showed no difference between groups, there was a significant increase of major or CRNM bleeding with the use of rivaroxaban. This increase was mainly presented as haematuria (9 vs 0), epistaxis (8 vs 1), and rectal bleeding (7 vs 2 events) (15).

Because of different CRNM bleeding definitions across trials, there was a wide variation in event rates, such as 3.8% incidence in RE-COVER II and a much higher incidence of 9.5% in EINSTEIN-PE. Major and CRNM bleeding were significantly reduced in those receiving dabigatran, but not rivaroxaban when compared with standard of care (10).

According to the data collected in the study investigating the use of NOACs in thromboprophylaxis after joint-replacement surgery (20), risk difference (RD) between the two drugs indicates a small and insignificant benefit in favour of rivaroxaban. At the same time, RD regarding major or CRNM bleeding indicates a difference that disfavours direct factor Xa inhibitor and which, although of borderline significance, indicates a true difference between treatments in this study (20).

Apart from bleeding complications, dyspepsia was the major side effect of dabigatran (10, 12). Proton pump inhibitors, used to treat dyspepsia, reduce absorption of dabigatran for 30% (11). Dabigatran doesn't have to be taken with food; on the other side, taking rivaroxaban without food decreases its absorption by 39% (11), which may lead to subtherapeutic plasma concentrations. Since NOACs have shorter half-life (<24h) than OACs (36-42h), suboptimal adherence of rivaroxaban or dabigatran may be more dangerous. Advanced liver disease is a contraindication to rivaroxaban use (21).

Renal elimination is higher in dabigatran comparing to rivaroxaban; therefore, using direct thrombin inhibitor is contraindicated in severe renal insufficiency (CrCl < 30mL/min) while taking direct factor Xa inhibitor is not recommended if CrCl < 15mL/min (11). Dose adjustment might be needed in some cases. Due to differences in renal excretion, hemodialysis can be used to treat overdosing with dabigatran, eliminating 50-60% of circulating dosage, which cannot be applied to rivaroxaban (9). Administration of activated charcoal may be useful to reduce absorption of rivaroxaban if taken less than six hours after overdose or accidental ingestion (8).

If bleeding continues or is life threatening, procoagulants, such as factor VIIa or prothrombin complex concentrates (activated or inactivated) can be administered, although the evidence of their effectiveness is limited (22). Highly specific antidotes for factor Xa and direct thrombin inhibitors are under development and might be available during upcoming years (23).

Furthermore, twice-daily dosing schedule of dabigatran might be more difficult for some patients to adhere to a daily regimen in contrary to rivaroxaban, which is used once daily. A dose adjustment needed at day 21 with the use of rivaroxaban requires communication between healthcare provider and patient during transition period. Dabigatran does not require any dose alteration in the first weeks of therapy and may provide a simpler approach after patient discharge. However, lead-in with parenteral anticoagulant therapy in case of dabigatran can be uncomfortable for some patients.

Perhaps the most interesting difference between Xarelto® and Pradaxa® is the incidence of arterial thrombosis. Whereas the rivaroxaban seems to be superior to other anticoagulants, the dabitragan elevates the risk of arterial thrombosis (24). Rivaroxaban also decreases the risk of myocardial infarction relative to warfarin (25) whereas dabigatran slightly increases this risk (26). The differences suggest that factor Xa inhibition may be more effective than thrombin inhibition in arterial circulation.

As low molecular weight drugs, rivaroxaban and dabigatan pass through placental barrier and therefore are contraindicated to be used in pregnancy (22). In women with child bearing potential, NOACs must be prescribed with contraceptive pills and used with caution.

Elderly population deserves brief discussion. The incidence of VTE rises exponentially in older adults (6). Older patients are also more likely to have various comorbidities, such as cancer, renal impairment, higher risk of bleeding or they use P-glycoprotein (P-gp) or CYP3A4 inducers/inhibitors. Therapy with NOACs in elderly patients with DVT and PE should be done carefully. As the average age of patients in conducted studies ranged from 55 to 58 years, efficacy and safety of rivaroxaban and dabigatran use in this group remain unclear.

Conclusion

VTE takes an important place in vascular surgery, with significant morbidity and mortality rates. It also represents an expensive condition to treat. By evidences based on literature and trials investigating clinical use of rivaroxaban and dabagatran, none of them seemed dominant over the other. Benefits such as lower therapy price, oral use and greater comfort for patients and healthcare providers place NOACs to frontline of VTE treatment. We need head to-head studies to have more clear picture of these two drugs; until then, clinicians will be forced to make treatment decisions based on their own experience.

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THE IMPACT OF DONOR ORGAN QUALITY ON THE OUTCOME OF A DECEASED DONOR KIDNEY TRANSPLANTATION

UTICAJ KVALITETA ORGANA NA ISHOD KADAVERIČNE TRANSPLANTACIJE BUBREGA

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Summary

Increasing disparity between the limited supply of deceased donor organs and the rising demand for kidneys has led to considering alternative strategies for expanding the availability of organs for transplantation.

The first definition of expanded criteria donor contained four different donor risk factors for graft failure: age, history of hypertension, cerebrovascular accident as a cause of death and final pre-procurement creatinine > 133μmol/l. Marginal donors are also those with diabetes or those with anatomical abnormalities.

Other factors such as donor maintenance, surgeon related factors, perfusion and transportation of organs also have an influence on donor organ quality.

The survival benefits seen in recipients of marginal kidney transplants are inferior compared to those in recipients of standard criteria donor kidneys, but significantly better than in those remaining on kidney waiting list.

Key words: kidney transplantation, expanded criteria donor, outcome.

Sažetak

Narastajući disparitet broja raspoloživih i potrebnih organa za transplantaciju podstakao je razmatranje alternativnih strategija za povećanje dostupnosti organa za transplantaciju.

Prva definicija marginalnog donora obuhvatila je četiri faktora rizika za insuficijenciju alografta bubrega: starost, podatak o prethodnoj hipertenziji, cerebrovaskularni insult kao uzrok smrti i terminalni kreatinin> 133μmol/l. Marginalni donori su i oni sa dijabetesom ili anatomskim abnormalnostima bubrega.

Na kvalitet organa utiču i faktori koji se odnose na održavanje donora, hiruški faktori, način perfuzije i transporta organa.

U odnosu na primaoce organa standardnog kvaliteta, primaoci organa marginalnih donora imaju kraće preživljavanje, ali je njihovo preživljavanje bolje u poređenju sa preživljavanjem bolesnika koji ostaju na listi čekanja za transplantaciju bubrega.

Ključne reči: transplantacija bubrega, marginalni donor, ishod

Uvod

Potreba za prevazilaženjem narastajućeg dispariteta između broja potrebnih i raspoloživih organa za transplantaciju je kao jedno od mogućih rešenja podstakla korišćenje organa suboptimalnih donora, kao što su stariji donori, donori sa komorbiditetima poput hipertenzije i dijabetesa ili donora sa povišenom koncentracijom serumskog kreatinina u vreme eksplantacije.

U današnje vreme definicija subotimalnog donora nije jedinstvena. U praksi takođe nema jedinstvenog stava za prihvatanje ili odbacivanje organa marginalnih donora, pa jedni transplantacioni centri prihvataju organe koje drugi centri proglašavaju neprihvatljivim.

Klinička procena kvaliteta organa

Prvu definiciju donora bubrega na osnovu proširenih kriterijuma („expanded criteria donors"- ECD) su predložili eksperti Nacionalne mreže za razmenu organa Sjedinjenih Američkih Država („United Network for Organ Sharing"- UNOS) 2001. godine. Ova definicija je izvedena na osnovu 4 faktora rizika lošijeg preživljavanja alografta bubrega kao što su starost donora, podatak o prethodnoj hipertenziji, cerebrovaskularni insult kao uzrok smrti i povišen terminalni kreatinin, odnosno kreatinin u vreme eksplantacije (7). Marginalni donor je definisan kao onaj čiji organi imaju najmanje 1,7 puta veći relativni rizik gubitka funkcije na osnovu prisustva pomenutih faktora rizika u odnosu na organe donora standardnog kvaliteta. Standardni kvalitet donora podrazumeva starost donora izmedju 10-39 godina, bez podatka o hipertenziji, da uzrok smrti nije cerebrovaskularni insult i da je terminalni kreatinin u referentnom

opsegu (9). Prema ovoj definiciji, svi donori staiji od 60 godina i oni uzrasta od 50-59 godina sa najmanje dva od preostala tri faktora rizika su zadovoljavali kriterijume marginalnog donora. U slučaju transplantacije organa od ECD donora, ne samo da je slabije preživljavanje alografta, već su učestalije i druge komplikacije, kao što je odložena funkcija grafta („Delayed graft function"- DGF). Međutim, preživljavanje bolesnika kojima su presađeni organi od ECD donora se ne razlikuje značajno u odnosu na primaoce organa standardnog kvaliteta, a duže je u odnosu na preživljavanje bolesnika koji ostaju na listi čekanja za transplantaciju (13). Zbog toga se smatra da je ishod transplantacije bubrega od marginalnih donora prihvatljiv, uz uslov da se sprovede adekvatan izbor primaoca i da se svi postupci od održavanja potencijalnog donora do implantacije organa optimizuju (23).

Posle masovnijeg korišćenja organa ECD donora u praksi, nastao je veći broj dopunjenih i preciznijih definicija. Stratifikovan Nybergov skor donora umesto 4, uzima u obzir 7 parametara koji podrazumevaju osobine donora i postupka transplantacije kao što su starost, podatak o hipertenziji i dijabetesu, uzrok smrti, terminalni kreatinin, vreme hladne ishemije (CIT) i promene na arterijama bubrega (12). Stratifikacija podrazumeva klasifikaciju organa na 4 kategorije kvaliteta (A, B, C, D) prema ukupnom broju bodova koji su dodeljeni na osnovu 7 prethodno pomenutih parametara. Transplantacija organa kategorije D praćena je najvećom učestalošću DGF, dužim trajanjem hospitalizacije, većom cenom lečenja i slabijom funkcijom alografta u prvih 30 dana posle transplantacije. Ista grupa autora je u cilju jednostavnije implementacije skora, a na osnovu analize podataka iz baze UNOS-a, naknadno smanjila broj faktora rizika koji ulaze u ukupnu vrednost skora na 5 najznačajnijih, u koje se ubrajaju starost donora, podatak o hipertenziji, uzrok smrti, terminalni kreatinin i HLA podudarnost (11).

Implementacija koncepta marginalnog donora u praksi je povećala broj transplantacija, ali nedovoljno da se obezbedi dovoljan broj organa za sve bolesnike na listama čekanja. Jedno od važnih pitanja koje je pratilo korišćenje ovakvih organa je izbor primaoca. U početku, dodela organa marginalnih donora je podrazumevala volju primaoca da ih prihvate, ali i njihovo pravo da budu informisani o proceni stepena funkcionalnosti i dugovečnosti organa koji prihvataju. Primaoci kojima su dodeljeni organi marginalnih donora u većem procentu su bili stariji od 50 godina u odnosu na primaoce organa standardnih donora (9). Pessione skor je po prvi put ukazao da rizik gubitka grafta zavisi od osobina donora i primaoca i definisao ga na osnovu kombinacije osobina donora (hipertenzija, cerebrovaskularni insult, povišen terminalni kreatinin) i starosti primaoca (14).

Novina koja je uvedena sa definisanjem Indeksa rizika donora („Donor Risk Index"- DRI) je stratifikacija verovatnoće dvogodišnjeg poluživota grafta u 5 grupa na osnovu 7 parametara od kojih su neki osobine donora (rasa, hipertenzija, dijabetes, cerebrovaskularni insult), postupka transplantacije (hladna ishemija) ili odnosa izmedju donora i primaoca (HLA podudarnost, podudarnost citomegalovirusnog statusa donora i primaoca) (20). Organospecifični indeks rizika donora („ Kidney Donor Risk Index"- KDRI) procenjuje rizik gubitka funkcije alografta bubrega na osnovu brojnih osobina donora i postupka transplantacije, kao što su starost donora, rasa, podatak o hipertenziji i dijabetesu, serumski kreatinin, cerebrovaskularni insult kao uzrok smrti donora, visina, težina, srčani zastoj, hepatitis C, HLA podudarnost na B i DR lokusu, CIT i dvostruka implantacija (16). Ovaj indeks odražava relativni rizik gubitka alografta bubrega u poređenju sa idealnim alograftom koji potiče od donora starosti 40 godina i bez prisutnih komorbiditeta.

Indeks profila donora bubrega („Kidney Donor Profile Index"- KDPI) poredi relativni rizik za nastanak insuficijencije alografta određenog donora sa alograftom koji potiče od prosečnog donora eksplantiranog tokom godine koja prethodi transplantaciji, a na osnovu starosti, težine, visine, rase, podatka o hipertenziji, dijabetesu i njihovom trajanju, uzroku smrti, serumskom kreatininu i prisustvu antitela na hepatitis C virus (3). Ovaj bodovni sistem se aktuelno koristi u sistemu raspodele organa u Sjedinjenim Američkim Državama, gde se najkvalitetniji bubrezi (KDPI <20%) dodeljuju primaocima sa najdužim procenjenim posttransplantacionim preživljavanjem.

Patohistološka procena kvaliteta organa

Krajem devedesetih godina pojavljuju se i patohistološki bodovni sistemi za analizu tkiva bubrega uzetog tokom eksplantacije, sa ciljem detaljnije evaluacije bubrega uzetih prvenstveno od starijih donora. Patohistološka analiza tkiva bubrega u vreme eksplantacije je prepoznata kao procedura koja nudi mogućnost donošenja odluka da li organ iskoristiti za transplantaciju ili odbaciti, ako se bubrezi prihvate da li uraditi jednostruku ili dvostruku implantaciju, kakvom primaocu ga implantirati, ali i u cilju dobijanja referentnog materijala za poređenje tokom kasnijih biopsija.

Za sve patohistološke bodovne sisteme zajedničko je da procenu zasnivaju na procentu sklerotičnih glomerula, stepenu hroničnih promena tubulointersticijuma i hroničnih promena na krvnim sudovima. Remuzzi-jev skor se izračunava na osnovu izraženosti glomerulske skleroze, tubulske atrofije, intersticijalne fibroze i promena krvnih sudova bubrega. Ukupna vrednost skora 1, 2 i 3 dalji postupak usmerava u pravcu implantacije jednog bubrega jednom primaocu, vredmost skora 4, 5 i

6 upućuje na implantaciju oba bubrega istog donora jednom primaocu, a vrednosti 7-12 ukazuju na potrebu da se organ ne prihvati za transplantaciju (17). U patohistološke skorove ubraja se i Karpinski skor, koji za razliku od prethodnog veći značaj pridaje promenama krvnih sudova bubrega u odnosu na ostale promene, zbog njihovog dokazanog uticaja na veću učestalost DGF i slabije jednogodišnje preživljavanje alokalema bubrega (5).

Kliničko-patohistološki bodovni sistemi za procenu kvaliteta bubrega donora nastali su na osnovu rezultata koji sugerišu da na jednogodišnju funkciju alografta najveći uticaj imaju kombinacija hipertenzije donora, terminalnog kreatinina ≥150 μmol/l i glomeruloskleroze (1).

Ideja ovih bodovnih sistema je bila da se popravi selekcija bubrega na osnovu podataka dostupnih u vreme eksplantacije, ali i da se unapredi selekcija primaoca u cilju boljeg uklapanja osobina donora i primaoca.

Nedostatak svih prethodno pomenutih bodovnih sistema je što ne uzimaju u obzir uticaj oštećenja organa tokom moždane smrti na kvalitet organa i njihovo dugogodišnje preživljavanje (10). Uticaj nepovoljnih efekata moždane smrti na kvalitet marginalnih organa je potencijalno veći, pa je mogućnost njihovog umanjenja posebno značajna u podgrupi ECD donora.

Uticaj moždane smrti donora na kvalitet organa

Moždana smrt predstavlja ekstenzivno i ireverzibilno oštećenje centralnog nervnog sistema zbog traume, cerebrovaskularnog insulta ili anoksije, koje ima brojne patofiziološke posledice na organe donora, a najznačajniji su hemodinamski poremećaji i hormonski disbalans. Hemodinamka nestabilnost se javlja kod skoro 90% donora, a oko 40% donora je hipotenzivno i uprkos primeni visokih doza inotropa (15). Hipotenzija donora duža od 3 časa povećava rizik akutnih odbacivanja (AO), a izaziva i izraženiju ishemiju organa (18). Hormonske promene koje se javljaju tokom moždane smrti podrazumevaju oslobađanje kateholamina, što zbog periferne vazokonstrikcije doprinosi ishemiji organa. Zbog disfunkcije prednjeg i zadnjeg režnja hipofize, kod oko 80% donora se javlja insipidni diajbetes, a snižena je i sekrecija tireoidnih hormona i kortizola, što se negativno odražava na kvalitet organa.

Moždana smrt ne izaziva samo ishemiju, već i inflamaciju organa donora, koja utiče na njihovu imunogenost posle transplantacije. U bubregu kadaveričnih donora se u većoj meri eksprimiraju adhezivni molekuli i HLA-DR molekuli (21). Organi donora sa većom ekspresijom aloantigena posle transplantacije indukuju češće epizode AO.

Moždana smrt izaziva i nespecifičnu inflamaciju koja participira u oštećenju organa posle transplantacije. Inflamacija se povećava sa trajanjem moždane smrti i izraženija je u slučaju hemodinamske nestabilnosti donora (25). Zbog nespesifičnih inflamatornih promena alografta tokom moždane smrti, posle transplantacije se brže razvijaju glomeruloskleroza i intersticijalna fibroza, što je u osnovi hronične nefropatije alokalema (HNA).

Oštećenja organa koja se javljaju tokom moždane smrti su najvećim delom klinički neprepoznatljiva. Manifestno akutno bubrežno oštećenje sa porastom serumskog kreatinina se javlja kod 10-15% moždano mrtvih donora, što je značajno manje u odnosu na istu pojavu kod ostalih bolesnika u jedinicama intenzivnog lečenja (22). Povišen terminalni kreatinin utiče na veću učestalost ranih komplikacija, kao što je DGF, ali je bez uticaja na dugoročno preživljavanje alografta (24)

Među uzrocima moždane smrti najnepovoljniji uticaj na ishod transplantacije ima cerebrovaskularni insult. Ukoliko je uzrok moždane smrti traumatski, ređe se javlja DGF, uspostavlja se bolja funkcije grafta posle prvog posttransplantacionog meseca i bolje je njegovo dugoročno preživljavanje (8).

Uticaj terapije donora na kvalitet organa

Pre dijagnoze moždane smrti, terapijski postupci imaju za cilj da povećaju šansu preživljavanja bolesnika. Posle moždane smrti, terapiju je potrebno usmeriti ka postizanju što boljeg kvaliteta organa koji se potencijalno mogu transplantirati.

Primena dopamina kod donora ima povoljne efekte na ishod transplantacije bubrega. Mehanizam protektivnog dejstva dopamina na bubreg ogleda se u popravljanju hemodinamike donora i umanjenju ishemičnih promena tokom moždane smrti i kasnije tokom prezervacije organa. Povećanjem hemodinamske stabilnosti donora, dopamin utiče na manju učestalost DGF, što je praćeno manjom potrebom za posttransplantacionim hemodijalizama (19). Zahvaljujući strukturi svog molekula koji sadrži dihidroksi-fenolni prsten, dopamin deluje i direktno protektivno na ćelijsku membranu tubulocita, pa je tubulska nekroza koja nastaje kao posledica ishemije manje izražena. Pozitivan uticaj dopamina je izraženiji u slučaju transplantacija izvršenih posle duže hladne ishemje (6). Primena dopamina kod donora tokom moždane smrti smanjuje i inflamatorne promene u bubregu i time pozitivno utiče na ranu funkciju alografta (2).

Hormonska terapija tokom održavanja potencijalnih donora podrazumeva primenu kortikosteroida, tireoidnih hormona, antidiuretskog hormona i insulina, poje-

dinačno ili u kombinaciji. Primena metil-prednizolona 3 sata pre eksplantacije, bez obzira na vreme nastanka moždane smrti, suprimira inflamaciju u tkivu bubrega (4).

Zaključak

Na kvalitet organa za transplantaciju utiče veliki broj faktora. Za razliku od nepromenljivih faktora kao što su starost donora, komorbiditeti i uzrok smrti, koji su sve prisutniji kod donora, zbog težnje da se obezbedi veći broj organa, adekvatnim terapijskim pristupom tokom održavanja donora se umanjuju potencijalna ošetećenja i utiče na bolji ishod transplantacije bubrega. Procena dugovečnosti alografta bubrega pre transplantacije je pretpostavka optimalnog izbora primaoca u cilju racionalnog korišćenja organa dostupnih za transplantaciju.

Napomena

Rad je usmeno izložen na mini simpozijumu organizovanom povodom 40 godina transplantacije bubrega u Kliničkom centru Srbije na 44. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 09.12.2015. godine.

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NEUROGENESIS AND THE IMPACT OF STEROID HORMONES ON BEHAVIOUR

NEUROGENEZA I UTICAJ STEROIDNIH HORMONA NA PONAŠANJE

Bojana Rankov Petrović[1], Aleksandra Rašić Marković[1], Dragan Hrnčić[1], Olivera Stanojlović[1]

Summary

It took almost a century to get over the dogma of impossibility of adult neurogenesis. A growing number of researches in the past few decades have brought phenomena of adult neurogenesis into light. Ideas of therapeutic possibilities of neural stem cells in managing brain stroke, traumatic brain and spinal cord injury, as well as growing number of neurodegenerative diseases, represent the basis of huge research projects.

After the development of CNS is finished, neurogenesis continues in two regions of the adult brain: sub ventricular zone of lateral ventricles and sub granular zone of dentate gyri of hippocampus. The process of neurogenesis brings two main questions concerning the regulatory mechanism: which factors enhance or suppress it and what is the significance of the process in humans. Brain development is under crucial influence of steroid hormones (effects are mediated through gene interaction or by neuromodulation of ion channel), so their influence on behaviour cannot be neglected. Studies have shown that hormones modulate learning and memory, but the specific roles of each of them should be monitored under a wide context of time, pre-exposition test manipulation, training as well as type of testing. Stress is another important factor in the regulation of adult neurogenesis, but current results highlight the importance of the opposite direction as well and young neurons interaction activity with HPA axis.

Neurosteroids (allopregnanolone, dihydroepiandrosterone) are synthetized in the brain, and their concentrations are found higher than in blood of mammals. A number of steroidogenic enzymes (rate limiting enzymes in synthesis from cholesterol) are targeted in the brain, spinal cord and peripheral nervous system. The significance of neurosteroids' existence in brain tissue is explored through experiments of epileptogenesis.

Numerous researches are trying to determine whether and how hormone alterations in neuroplasticity and neurogenesis are related to changes in cognition. Progesterone has been shown to improve neurologic outcome in multiple experimental models but it failed to show effect through two phase III clinical trials in patients with traumatic brain injury.

Keywords: neurogenesis, steroid hormones, cognition, stress, epileptogenesis.

Sažetak

Potreban je bio skoro čitav vek da bi dogma o nemogućnosti proliferacije i regeneracije unutar centralnog nervnog sistema (CNS) odraslih jedinki bila prevaziđena. Zahvaljujući velikom broju istraživanja u poslednje tri decenije, fenomen neurogeneze kod čoveka postao je nepobitna činjenica. Ideje o mogućim terapijskim implikacijama neuralnih stem ćelija u lečenju moždanog udara, traumatskog oštećenja mozga i kičmene moždine kao i neurodegenerativnih oboljenja osnova su velikih istraživačkih projekata

Nakon završetka razvoja CNS-a, neurogeneza se u odraslih jedinki kontinuirano nastavlja u dva regiona mozga: subventrikularnoj zoni lateralnih komora i subgranularnoj zoni dentatnog girusa hipokamusa. Proces neurogeneze nameće bazična pitanja o regulatornim mehanizmima koji je podstiču ili suprimiraju, kao i pitanja o funkcionalnom značaju kod čoveka. Razvoj mozga od embrionalnog stadijuma do odraslog doba je pod uticajem steroidnih hormona (efekte ostvaruju genskom interakcijom ili neuromodulatornom ulogom preko jonskih kanala) te je izvestan efekat i u ponašanju jedinke. Studije ukazuju da gonadalni hormoni značajno utiču na procese učenja i pamćenja, ali bi relativna uloga ovih hormona ponaosob morala da bude protumačena u širem kontekstu vremena administracije, preekspozicionom treningu kao i tipu testa. Uticaj stresa je prepoznat takođe kao značajan činilac adultne neurogeneze, a najnovija funkcionalna ispitivanja ukazuju i na značaj suprotne rakcije, tj. uticaja mladih neurona na aktivnost hipotalamo-hipofizno-gonadne osovine i odgovora na stres.

Neurosteroidi (alopregnenolon, dihidroepiandrosteron) se sintetišu u samom moždanom tkivu gde su nadjeni u većim koncentracijama nego u krvi sisara. Brojni steroidogeni enzimi (važni u konverziji holesterola do neurosteroida) su targetovani u mozgu, kičmenoj moždini i delovima perifernog nervnog sistema. Značajan efekat neurosteroida pokazan je u procesima epileptogeneze.

Brojne studije pokušavaju da odgovore na pitanje u kojoj meri je neurogeneza i preživljavanje neurona u funkciji kognicije uslovljena i uticajem hormona. Eksperimentalno potvrđene regenerativne sposobnosti progesterona su upotrebljene kroz III fazu kliničkih ispitivanja kod pacijenata sa traumatskim oštećenjem mozga.

Ključne reči: neurogeneza, steroidni hormoni, kognicija, stres, epileptogeneza

Neurogeneza: istorijske perspektive i opšta razmatranja

Početkom dvadesetog veka Cajal S.R., je zapiso: „U zrelim centrima, nervni putevi su nešto zaustavljeno, završeno i nepromenljivo. Sve može da umre, nista se ne regeneriše“ (1). Sa početka 21. veka doktrina je promenjena, zapravo neurogeneza je definisana kao proces stvaranja novih nervnih ćelija u mozgu odrasle jedinke iz neuralnih stem ćelija (NSĆ) (2).

Sve do kraja XX veka centralna pretpostavka neuronauke ogledala se u vidjenju čuvenog naučnika Santiago

Ramon y Cajala (1, 3, 4), da se stvaranje novih nervnih ćelija završava u ranom postnatalnom periodu. Uprkos tome što je Allen E., već 1912. god (5), dala nagoveštaj dokaza o postojanju adultne neurogeneze uočivši mitotička vretena u ćelijama zida lateralnih komora kod Wistar albino pacova starih 120 dana, nalazi su ostali neprimetni za neuronaučno društvo. Tek 60. godina ideja o postojanju neurogeneze potkrepljena je novootkrivenim naučnim činjenicama. Koristeći radioaktivni 3H-timidin, nukleozid koji ćelije preuzimaju u S fazi pripreme za mitozu, Alltman J. (6, 7) autoradiografski identifikuje proliferišuće neurone u dentatnom girusu himpokampusa kod odraslih pacova. Alltman prvi ukazuje i na postojanje neuralnih stem ćelija u subventrikularnoj zoni lateralnih komora (SVZ) (7) i detaljno opisuje njihovu migraciju do olfaktivnog bulbusa (OB) gde sazrevaju u neurone (8).Validnost ovih rezultata osporena je nedostatkom dokaza da se zaista radi o proliferišućim neuronima. Kaplan M. je potkrepio Alltmanove rezultate tehnikom elektronske mikroskopije, čime je morfološki potvrdio neuronsku prirodu autoradiografski obeleženih ćelija petnaest godina kasnije (9-11).

Uprkos objavljivanju rezultata u najprestižnijim časopisima, zbog ograničenih tehničkih uslova tadašnjeg doba, nepostojanja imunohistohemijskih metoda i time funkcionalne identifikacije ćelija, neurogeneza je trpela kontinuirani skepticizam (12). U prilog tome, vodeći naučnik u oblasti neurorazvoja, Rakić P., (1985. g) objavio je rezultate istraživanja na Resus majmunima dobijene takodje autoradiografskim beleženjem timidinom. Rakić nije identifikovao niti jednu obeleženu ćeliju sa morfološkim osobinama neurona u ispitivanim strukturama mozga (13). Iz tih razloga, izneo je zaključke da su kod odraslih primata stabilne neuronske populacije biološki neophodne za organizam čije preživljavanje počiva na naučenom ponašanju, sticanom tokom dugog vremena. Navedeno je tada, takođe, da socijalno i kognitivno ponašanje primata zahteva odsustvo neurogeneze (14-16). Razvoj tehnike omogućio je da istorija rada čuvenog skeptika neurogeneze, Rakića P., nedugo potom bude ispisana potvrdnim dokazima o postojanju adultne neurogeneze u dentatnom girusu primata (17).

Sa druge strane, '80tih godina Nottebom F. i saradnici započeli su istraživanja neuronske osnove učenja pesama kod ptica i otkrili izrazitu promenljivost veličine dva jedra koja su bila definisana kao krucijelna u ovom procesu (18). Obeležavanjem radioaktivnim timidinom uočeno je postojanje neurogeneze u njima kao i zavisnost te pojave od pola jedinke i godišnjeg doba u kom je istraživanje rađeno (19). Došlo se do zaključka da je testosteron preko moždanog neurotrofičkog faktora (engl. *brain derived neurotrofic factor, BDNF*) bio upravo odgovoran kako za stvaranje novih neurona, tako i za njihovo preživljavanje i funkcionalnu integraciju (20-22).

Neuralne stem ćelije: poreklo, regulacija aktivnosti

Adultne neuralne stem ćelije definisane su njihovom sposobnošću za samoobnavljanjem i diferencijacijom u neurone, astrocite i oligodendrocite (2,23). Naše razumevanje biologije adultnih neuralnih stem ćelja i neurogeneze nastalo je u najvećoj meri zahvaljujći istraživanjima na glodarima (24). Neurogeneza je nedvosmisleno potvrđena u dva regiona mozga: subventrikularnoj zoni lateralnih komora (SVZ) i subgranularnoj zoni (SGZ) dentatnog girusa hipokampusa (25, 26). Neuralne stem ćelje u SVZ i SGZ, iako dele mnoge sličnosti, predstavljaju dve populacije ćelija koje se značajno razlikuju kako u njihovom razvoju i organizaciji tako i u funkciji. U oba slučaja, NSĆ su astrocitima-slične ćelije kako morfološki, tako i eksprimacijom astrocitnog molekularnog markera-glijalni fibrilarni kiseli protein (engl. *glial fibrillary acidic protein, GFAP*) (27-30).

U subventrikularnoj zoni lateralnih komora, NSĆ se nazivaju B tipom ćelija, koje nakon aktivacije vrše *up*-regulaciju receptora za epidermalni faktor rasta i progenitorski marker nestin, a potom se dele dajući tranzitorni tip ćelija C, koje se potom diferenciraju u tip A neuroblaste. Neuroblasti, identifikovani beleženjem *doublecortinom*, napuštaju SVZ i ekstenzivnom migracijom putem rostralne migratorne trake dolaze do OB gde sazrevaju u GABAergičke interneurone (31-34). Postojanje sličnog migratornog puta u mozgu odraslog čoveka vrlo je kontraverzna tema. Jasno je pokazano postojanje migracije neuroblasta iz zidova lateralnih komora u olfaktivnom traktu humanog fetalnog mozga, ipak pretpostavka je da ista sa razvojem prestaje (35). S obzirom da je SVZ najveći germinativni centar u mozgu odraslih sisara (36), postavljaju se fundamentalna pitanja: koja je funkcija neurogeneze u SVZ kod čoveka i da li istaživačke mogućnosti današnjice mogu da dopru do adekvatne spoznaje.

Sa druge strane, zahvaljujući specifičnoj morfologiji i jedinstvenom setu molekularnih markera, u SGZ su identifikovana dva tipa neuralnih progenitora. Ćelije tipa 1 eksprimiraju markere karakteristične za astrocite: nestin, GFAP, Sox2 (37-39) i dr. Ipak, morfološki i funkcionalno su vrlo različite od zrelih astrocita. Hipokampalni progenitor tip 2 ne eksprimira GFAP, a studije su pokazale da Sox2-pozitivne ćelije mogu da daju neurone i astrocite, što je predstavljao prvi *in vivo* dokaz stem ćelijskih osobina kod hipokampalnih progenitora (40). Istraživanja su pokazala da se u hipokampusu čoveka neurogeneza održava tokom čitavog života što je slučaj i u životinja (41-43).

Iako su tipovi neuralnih progenitora jasno definisani, do danas se ne zna sa sigurnošću koji faktori i u kojoj meri regulišu adultnu neurogenezu. Pretpostavke su da diferencijaciju u astrocite ili neuroblaste određuju

upravo ekstracelularni faktori neurogene niše u kojoj se NSĆ nalaze (44, 45). Kao odgovor na funkcionalne zahteve tj neuronsku stimulaciju, u ćelijama u diferencijaciji dolazi do aktiviranja seta ranih gena koji kodiraju transkripcione faktore koji pak regulišu ekspresiju gena uključenih u određivanje fenotipa budućih neurona (46). Pokazano je kasnije, da su upravo ovi geni odgovorni u procesima neuronske plastičnosti i konsolidacije pamćenja (47, 48). U *in vitro* uslovima je pokazano da oštećenje moždanog tkiva indukuje proliferaciju kortikalnih astrocita u neurone (49) dok u *in vivo* uslovima, nije poznato da astrociti osim procesa samoobnavljanja mogu da generišu drugu vrstu ćelija (neurone). Usled pomenutog procesa dolazi do stvaranja glijalnog ožiljka. Sa druge strane, identifikovano je da u odgovoru na moždani udar, ćelije prednjeg dela SVZ koje su inače u stanju mirovanja, generišu kako astrocite tako i neuroblaste koji potom migriraju na mesto insulta (50).

Neurogeneza kao proces, može biti poboljšana uticajem na proliferaciju progenitora, diferencijaciju i preživnjavanje diferentovanih ćelija. Mnogi faktori su prepoznati kao činioci u ovim procesima, a u velikoj meri se ispituje uticaj steroidnih hormona (51).

Hipokampus i kognitivne funkcije:odnos prema neurogenezi i gonadalnim hormonma

Efikasnost adultne neurogeneze podrazumeva dve komponente: broj novostvorenih ćelija, kao i broj preživelih ćelija u određenoj tački vremena. Nivo hipokampalne neuronske proliferacije je veći kod ženki (52), dok je preživljavanje ćelija veće kod jedinki muških glodara (53, 54). Zavaljujući razlikama u hormonskom statusu među polovima, jasno proizilazi njihov uticaj na adultnu neurogenezu (55). Brojne studije su pokazale da estradiol utiče na povećanje ćelijske proliferacije u SGZ, ali i na smanjenje preživljavanja novostvorenih neurona kod ženki glodara, te da ovi efekti zavise od doze i vremena administracije (56-58). Uticaj testosterona na proliferaciju neurona u SGZ kao i u SVZ takođe se pokazao pozitivnim, međutim pretpostavlja se da se ovi efekti ostvaruju preko estrogenskih receptora, zahvaljujući metaboličkoj konverziji testosterona u estrogen (59). Nasuprot tome, testosteron i njegov metabolit, dihidrotestosteron, deluju pozitivno na proliferaciju i preživljavanje ćelija aktiviranjem i androgenih receptora. Ovo se ne odnosi na dentatni girus, koji najverovatnije odgovara na stimulaciju estrogenskih receptora Erα i Erβ (60, 61). Umerena fizička aktivnost koja ima za posledicu sintezu dihidrotesterona stimuliše neurogenezu u adultnom hipokampusu (62). Pretpostavlja se da se ovi efekti ostvaruju preko NMDA glutamatskih receptora te aktivacijom sinteze BDNF i VEGF (engl. *vascular endotelial growth factor*) (63).

Funkcionalna integracija mladih neurona u postojeće neuronske krugove - adultna neurogeneza u hipokampusu i kognicija, danas su predmet sve većeg broja istraživanja (64, 65). Eksperimentalni radovi ukazuju da smanjen nivo neurogeneze redukuje sposobnost učenja i prostornog pamćenja (dugotrajno i kratkotrajno) (66, 67). Nasuprot jasnom odnosu neurogeneze i hipokampus-zavisnih oblika učenja i pamćenja, pokazano je da veći broj neurona nije siguran parametar boljeg ishoda u rešavanju kognitivnih testova (68). Uticaj gonadalnih hormona na procese neurogeneze i hipokampus-zavisne funkcije, uočen je u eksperimentima na ženkama glodara sa intaktnim estrusnim ciklusom (69, 70). Ženke pacova u proestrusu (visok estradiol i progesteron) imaju lošiji rezultat u testovima prostornog učenja (ispitivan na Morisovom vodenom lavirintu) u poređenju sa ženkama u estrusu (nizak estradiol) (71-73). Uloga stresa tokom proestrusa je verovatan razlog umanjenom značaju estrusnog ciklusa na performanse prostornog pamćenja (74).

S ozirom da kod ženki pacova i estrogen i progesteron fluktuiraju tokom estrusnog ciklusa, brojne studije su pokušale da nađu relativni doprinos svakog od ovih hormona na učenje i pamćenje. Chesler i Juraska (75) su našli da kod ovariektomisanih životinja administracija estradiola ili progesterona 4h pre testiranja u Morisovom vodenom lavirintu ne rezultira značajnim efektima, dok oba hormona administrirana zajedno utiču na lošiji ishod pamćenja. Za razliku od prethodnih studija, akutna administracija estradiola i progesterona odmah nakon treninga značajno poboljšava pamćenje pozicije objekta (74).

Brojnim testovim je pokazano da je ovariektomija asocirana sa lošijim kognitivnim funkcijama kod žena i ženki glodara (76-78) dok tretman estradiolom može da povrati smanjen nivo kognitivnih funkcija uzrokovanih ovariektomijom (80). Nauka ne bi bila interesantna da ne postoje oprečni rezultati: ovariektomija oštećuje prostornu kogniciju kod adultnih, dok je poboljšava kod starijih žena (81).

Adultna neurogeneza i veličina hipokampusa značajno su smanjeni u trudnoći (82) i kao posledica nastaje pad radne memorije i prostornog snalaženja u odnosu na negravidne žene (83). Oprečni zaključci isto dizajniranih studija ukazuju da rezultati testova zavise od pola fetusa (84). Zapravo, majke koje nose muški fetus imaju bolje rezultate na testovima (radne memorije i mentalne rotacije) i oni perzistiraju do 19 meseci nakon porođaja.

S obzirom na široku rasprostranjenost progesteronskih receptora na svim vrstama ćelija u nervnom sistemu, opravdan je njegov uticaj na ponašanje, emocije, zapaljenske reakcije, funkciju mitohondrija, neurogenezu i regeneraciju, mijelinizaciju i oporavak u modelima traumatskog oštećenja mozga (85). Verovanja u terapijske

mogućnosti progesterona sežu čak do III faze kliničkih studija traumatskog oštećenja mozga, gde se na žalost nije pokazao značajnim u odnosu na placebo (86, 87). Ipak, istraživanja sa ciljem boljeg dizajna studija i analize rezultata se nastavljaju.

Neurogeneza i stres

Hipokampus predstavlja strukturnu osnovu učenja, kontrolor i efektor je našeg pamćenja i prostorne navigacije dok, stres oblikuje emocije i ponašanje. Hipokampus učestvuje u kontroli stresa i raspoloženja, za koju je najverovatnije odgovorna neurogeneza (88). Sve navedeno je razlog što se uzrok određenim psihijatrijskim oboljenjima može naći u poremećenoj neurogenezi u hipokampusu (89). Jasno je definisan model depresije kod životinja izazvan blagim hroničnim stresom, čije se posledice na ćelijskom nivou ogledaju u smanjenoj neurogenezi (90). U eksperimentima gde je adultna neurogeneza bila smanjena bez primene stresa, životinje nisu pokazivale depresiji-slično ponašanje, čime je sugerisano da neurogeneza može imati modulatornu ulogu u odogovoru na stres (91). Nedavne studije ukazuju da zreli neuroni smanjuju neuroendokrini odgovor na stres tj. da vrše ulogu "amortizera stresa" (92).

Smanjena neurogeneza (transgena modifikacija ili izlaganje radijaciji), povećava nivo hormona koji čine odgovor na stres što potvrđuje smanjenje supresije glukokortikoida egzogenim deksametazonom kod neurogeneza-deficijentnih miševa (93). Adultna neurogeneza pojačava glukokokortikoidima posredovanu negativnu povratnu spregu u hipotalamo-hipofizno-gonadnoj osovini

Uticaj stresa na rezultate u bihejvioralnim testovima u mnogome zavisi od nivoa endogenih hormona koji je uslovljen periodom ciklusa u kom se ispitivana životinja nalazi. Reaktivnost na stres bila je mnogo veća kod ženki pacova u proestrusu u odnosu na jedinke u estrusu (94).

Uočeno je da akutni stress (izazvan nepoznatom sredinom i plivanjem u Morisovom vodenom lavirintu) negativno utiče na prostorno snalaženje ženki (95), dok stres izazvan imobilizacijom pozitivno utiče na prostorno pamćenje u Y lavirintu kako kod ženki u proestrusu tako i kod onih u estrusu (96). Neaverzivne aktivnosti kao što su fizička aktivnost, seksualno iskustvo i dr. koje uzrokuju akutno lučenje hormona stresa, takodje pozitivno utiču na adultnu neurogenezu (97, 98).

Jasno je da ne postoji jednostavan, linearan odnos između hormona stresa i adultne neurogenze. Adultna neurogeneza teoretski utiče na smanjenje stresnog odgovora i suštinski uspostavlja adekvatan dinamizam istog. Moglo bi se zaključiti, da disfunkcija ovih mehanizama doprinosi riziku nastanka depresije (99, 100).

Neurogeneza, hormoni i epileptogeneza

Epilepsije pokazuju značajne razlike u incidenci, progresiji, težini napada i odgovoru na terapiju među polovima. Efekti uticaja gonadalnih hormona tokom moždanog razvoja oslikavaju se permanentnim strukturnim razlikama među polovima (101). Ipak, precizni mehanizmi uticaja na razvoj moždanih struktura i neuronskih krugova odgovornih za razlike u kontroli moždane ekscitabilonosti i dalje su nejasni (102). Ciklične promene nivoa estrogena i progesterona veoma su važne u patogenezi katamenijalne epilepsije, oblika bolesti kod žena gde je prevalenca konvulzivnih napada zavisna od menstrualnog ciklusa (103). U najvećem broju istraživanja, uočeni su prokonvulzivni efekti estrogena, dok je administracija progesteron imala snažnu antiepileptičnu aktivnost (104). Nedavnom multicentričnom kliničkom studijom ispitani su terapijski efekti progesterona kod žena sa epilepsijom, a rezultati su pokazali značajno bolji odgovor kod žena sa perimenstrualnom egzacerbacijom simptoma u odnosu na kontole (105). Progesteron predstavlja jedan od intermedijernih prekursora u sintezi neurosteroida (106). Neurosteroidi (alopregnanolon, androstenedione, alotetrahidrodeoksikortikosteron -THDOC) pozitivnom alosteronom modulacijoim GABA-A receptora smanjuju ćelijsku ekscitabilnost (107). U našoj labaroatoriji su razvijeni metafitom indukovan, homocisteinski i lindanski modeli epilepsije, te ispitani brojni antikonvulzivni i prokonvulzivni faktori (108-113). Administracija alopregnanolola u homocisteinskom modelu epilepsije kod pacova nije dala očekivane antikonvulzivne efekte (neobjavljeni rezultati). Ispitivanja na ovom polju tek predstoje. S druge strane, pokazano je da administracija finasterida u modelu hepatične encefalopatije doprinosu povećanju ekspresije markera neurona i glije, kao i poboljšanju motornih i EEG fenomena. Istraživanja uticaja testosteron undekanoata na kogniciju (neurogenezu), epilepsiju, fizičku aktivnost, anksioznost, nocicepciju i metabolizam adultnih ženki pacova je u toku.

Zaključak

Uticaj steroidnih hormona na procese adultne neurogeneze je neizostavan. Kvantifikacija adultne neurogeneze u hipokampusu je pokazala da je oko trećina neurona sposobna za procese samoobnavljanja te da može da se izrazi sa 1,75% od ukupne neuronske populacije hipokampusa tokom jedne godine, i ovaj broj sa starenjem opada. Translacioni aspekti naših studija mogli bi imati značaj s obzirom na sve veću incidencu degenerativnih i psihijatrijskih oboljenja, moždanih udara kao i traumatskih povreda mozga i perifernih nerava.

Napomena

Rad je usmeno izložen na mini simpozijumu Translacioni aspekti eksperimentalnih modela u neurofiziologiji i neuroendokrinologiji na 44. simpozijumu Stremljenja i novine u medicini, Medicinski fakultet u Beogradu, 07.12.2015. godine.

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THE RELATIONSHIP BETWEEN GENERAL AGGRESSION MODEL AND COMORBIDITY OF ANTISOCIAL PERSONALITY DISORDER AND BIPOLAR AFFECTIVE DISORDER

POVEZANOST OPŠTEG MODELA AGRESIVNOSTI SA KOMORBIDITETOM ANTISOCIJALNOG POREMEĆAJA LIČNOSTI I BIPOLARNOG AFEKTIVNOG POREMEĆAJA

Viktorija Popović[1], Nikolina Banjanin[2], Milena Milanović[3] Aleksandar Damjanović[1,4]

Summary

The General Aggression Model (GAM model) is a dynamic, social and cognitive development model that includes situational, individual and biological variables, based on the theories of social learning and social cognitive theories, as well as on a large number of theoretical and empirical arguments of many authors who are engaged in the study of aggression. The subject of our interest is the phenomenon of aggression in patients with bipolar affective disorder with the presence of antisocial personality disorder. The combined factors of aggressiveness in GAM model can be used to determine the presence, intensity or prediction of aggression in these patients. The General Aggression Model provides the division factors of aggressiveness into direct and indirect, such as personality factors, situations, environmental factors and biological factors.

Keywords: General Aggression Model, antisocial personality disorder, bipolar affective disorder.

Sažetak

Opšti model agresivnosti (GAM model) je dinamički, socijalno kognitivni, razvojni model koji uključuje situacione, individualne i biološke varijable, a zasnovan je na teorijama socijalnog učenja i socijalno kognitivnim teorijama, kao i na osnovu velikog broja teorijskih i empirijskih argumentacija brojnih autora koji su se bavili proučavanjem agresivnosti. Predmet našeg intersovanja je fenomen agresivnosti kod pacijenata obolelih od bipolarnog afektivnog poremećaja sa prisustvom antisocijalnog poremećaja ličnosti. Objedinjeni faktori agresivnosti u GAM modelu se mogu koristiti za utvrđivanje prisustva, intenziteta ali i predikciju agresije kod pacijenata. Opšti model agresivnosti nudi podelu faktora agresivnosti na neposredne i posredne, odnosno na faktore ličnosti, situacije, sredinske faktore i biološke činioce.

Ključne reči: Opšti model agresivnosti, antisocijalni poremećaj ličnosti, bipolarni afektivni poremećaj

Introduction

Aggression is a personality trait that is most striking in people with antisocial personality disorder. Most authors define it as willingness to take action and behaviour with intent to cause injury to others or any sort of damage. According to some authors aggression is a learned behaviour, and it is learned in early years of child's development. Eron (1) often uses the terms aggression and violence interchangeably in his papers, which makes sense when it is considered the dominant content of antisocial personality disorder. The most common definition of violence that we find in literature (2) explains violence as specific behaviour of a person to other persons, including threats, attacks or both for the purpose of causing physical or psychological harm. Most of research deals with physical violence, probably because psychological violence is much harder to monitor, observe, measure. Both of these types of violence are essential features of a person suffering from antisocial personality disorder. The definition of aggression says that this is behaviour with intent to cause injury to another person. This definition is also used by Eron (1) as the definition of antisocial personality disorder in the research of acquiring aggressive behaviour. The author notes that we must distinguish between aggression in sport (when the sport takes place according to pre-determined rules), and in a war when some extremely aggressive behaviour patterns are more prosocial than antisocial coming from the aggressiveness of people with antisocial personality disorder.

Comorbidity of antisocial personality disorder and bipolar affective disorder

Mood disorders and personality disorders are often present at the same time thereby forming sometimes quite a different clinical picture in relation to the primary disorder. According to the criteria of the Tenth Revision of the International Classification of Diseases (3) bipolar affective disorder belongs to the group of mood disorder diseases characterized by episodes of elevated mood, increased energy and activity (mania and hypomania) and low mood accompanied by stages of grief and reduced activity (depression). The phases of mania

and depression alternate in the clinical picture of bipolar affective disorder and its basic characteristics. Antisocial personality disorder is classified in cluster "B" personality disorders according to the diagnostic criteria of the American Psychiatric Association (4). Antisocial personality disorder is defined by behavioural indicators such as violations of social and legal norms; manipulative behaviour, cheating, lying, impulsiveness, aggressiveness, recklessness, irresponsibility, insensitivity, etc.

In patients with bipolar affective disorder some of the personality disorders are often present. Antisocial personality disorder, according to some authors, (5) is relatively frequent with bipolar affective disorder. One of the main common characteristics of these disorders is aggressive behaviour, which becomes more radical and dangerous in destructive personality disorder such as antisocial personality disorder. Antisocial personality disorder is relatively frequent in this category of patients and we pointed out that a number of patients with bipolar affective disorder in the stages of mania and hypomania, which follows already high energy potential, also develop extreme forms of impulsive and aggressive behaviour, which is often in conflict with social and legal standards (6, 7).

Aggressive behaviour

Aggression is affected by social, psychodynamic and genetic factors. Aggressive behaviour in children and adults is a long process because no one becomes aggressive all of a sudden, or "gets aggressive behaviour". Aggressive behaviour is affected by a wide range of factors, such as genetic, neuroanatomical, endocrine, physiological impacts on society, family, peer group, abuse of opiates (8). Aggressive behaviour does not occur simply, it is not, as some people believe, a "childhood disease", but people who say so are "programmed" to think this way on the basis of previous experience and learning (1). Therefore, alternative prosocial behaviour is either not trained or is not trained as well as aggressive behaviour. Aggressiveness that is common at the beginning of adolescence is not the behaviour that occurs spontaneously (9). This behaviour had been prepared long before puberty, it was somewhere in that child's past, who is the product of the above mentioned biological, psychological and social factors. Person "somehow, somewhere learned to solve interpersonal problems, release themselves from frustration and obtain some benefit from aggressive behaviour" (1).

Studies of aggressive behaviour provide a large number of theories that explain different ways and factors of such behaviour. The most important theories of aggression are expressed through psychoanalytic view of aggression, etiological view of aggression, aggression frustrational theory, biological theory of aggression and learning theory of aggression and aggressive behaviour. Still, one of the most important theories of aggressive behaviour is the General Aggression Model (GAM model), which was presented by Anderson and Carnagey (10).

The General Aggression Model

Carnagey and Anderson (10) developed the theory of General Aggression Model (GAM model). It is a dynamic, social and cognitive development model that includes situational, individual and biological variables, based on the theories of social learning and social cognitive theories, as well as on a large number of theoretical and empirical arguments of many authors who have studied aggressiveness. This model is very interesting from the point of studying comorbid antisocial personality disorder and bipolar affective disorder because it covers a broad scientific area that deals with studies of aggressive behaviour, which is the main determinant of comorbidity of these disorders.

Violence or aggressive behaviour explained by Carnagey and Anderson (10) is different in different societies according to parameters such as: the availability of weapons; different cultural norms about aggressive behaviour; global warming; exposure to media that promote these sorts of behaviour (Internet, television, computer games). However, none of these factors is able to independently explain the phenomenon of violence and aggressive behaviour. The authors have an opinion that aggressive behaviour occurs in multi-environment as it is environment that offers a multitude of aggressive behaviour models (for repute and learning); frustrating and victimizing environment; environment that encourages aggressive behaviour and teaches people that aggressive behaviour is acceptable, desirable, and that it symbolizes social success.

Like other socio - psychological oriented authors, Anderson and Huesmann (11) see the problem of aggression as behaviour directed towards another individual with the intent to hurt them. In addition, to person who behaves that way must believe that by doing so he/she will hurt the target, and the target is motivated to avoid that behaviour. These authors make a right and clear distinction between aggressive behaviour and violence. Violence is usually defined as physical aggression that leads to extreme end such as murder or assault of high intensity. Any violence is aggression, but not every aggressive behaviour is violence (for example, a child who pushes another child with a bike is aggressive, but not violent). However, when it comes to shooting in schools, which these authors are extremely interested in because of increasingly frequent attacks in schools throughout the United States, it is both aggression and violence. Some authors often use such terms as synonyms in the

Table 1. Proximate causal factors in GAM model

Person	Situation
Unstable high self-esteem	Social stress
Narcissism	Provocation
Self-image	Frustration
Long-term goals	Pain/discomfort
Self-efficacy beliefs for violent and nonviolent behaviour	Bad moods
Normative beliefs about aggression and retaliation	Weapons
Attitudes toward violence	Violent scenes
Hostile attribution, expectation and perception bias	Violent media
Aggression scripts	Noise
Dehumanization of others	Temperature
Cultural stereotypes	Threatening and fearful stimuli
Moral justification	Exercise
Displacement of responsibility	Alcohol and other drugs

study of antisocial personality disorder, whereas others make a difference between them by giving sometimes too narrow a definition of violence (according to Anderson), meaning only a serious physical injury to another person through the perpetration of acts that are not legal. In its aggression dimensional model, Anderson (10) distinguishes the following dimensions that are basic characteristics of aggressiveness: the degree of hostility; automatism; the degree to which primary objective is to hurt the victim in relation to the benefits to the perpetrator; level of understanding the result.

Considering that there are direct and indirect causal factors of aggression, Carnagey and Anderson (10) see personality and situation as direct factors as well, whereas indirect factors are social environment and biological differences. The first factors are current and active in current social situations, while others show their influence after a long period of time.

Indirect factors affect strengthening of direct factors that lead to aggressive behaviour, or minimize the impact on those direct factors that inhibit aggression. As they state, the indirect factors affect willingness of an individual to realize aggressive behaviour. In their considerations it can be noticed that some biological and environmental factors appear both as direct and as indirect factors at the same time, which highlights the problem of aggression in patients with comorbid antisocial personality disorder and bipolar affective disorder.

The subject of our interest is the phenomenon of aggressive behaviour in patients with bipolar affective disorder with the presence of antisocial personality disorder, because we can use factors of aggression in GAM model that can be used to determine the presence and intensity, but also the prediction of aggression in these patients. General Aggressive Model offers a division factors of aggressiveness on the direct and indirect factors, as well as personality factors, situations, environmental factors and biological factors.

As direct causal factors, the authors distinguish personality and situation. Under the factor of personality in General Aggression Model there are: unrealistically high self-esteem; narcissism; egotism; lack of long-term goals; ability to distinguish between aggressive and non-aggressive behaviour; the presence of normative beliefs about aggression and positive attitudes in general about the aggressiveness and violence; hostility and hostile expectations and perceptions; aggressive scripts; dehumanization of others; cultural stereotypes; disorders of moral judgment and displacement of responsibility. Situation factor means: social stress; provocation; frustration; pain and discomfort; bad mood; possession and availability of weapons; violent scenes and violent media; noise; high outdoor temperature; a threatening or fearful stimuli, alcohol and drugs (Table 1).

Carnagey and Anderson (10) include environmental and biological factors into indirect causal factors. Environmental factors that stand out are the following: dysfunctional families; inadequate parental functions; poor and violent neighbourhoods; cultural norms that support violence and aggressive behaviour; the experience of the victim; deprivation; difficult living conditions; conflicts in the group; traumatic, terrible events; lack of persons who would react in violent situations; diffusion of responsibility; exposure to aggression and violence by media; contact and hanging out with antisocial and problematic people. Biological factors are related to low levels of excitation; low serotonin; presence of ADHD (attention deficit hyperactivity disorder); hormonal imbalance; as well as the deficit function of performance (Table 2).

GAM model is based on numerous theories of aggressiveness (12, 13, 14, 15, 16) and through it refracts personality factors and social environment factors which are

Table 2. Distal causal factors in GAM model

Environmental modifiers	Biological modifiers
Maladaptive families and parenting	Low arousal
Violent neighbourhood	Low serotonin
Cultural norms that support violence	ADHD
Victimization experiences	Hormone imbalances
Deprivation	Executive functioning deficits
Difficult life conditions	
Group conflict	
Fear including events	
Lack of bystander intervention in violent encounters	
Diffusion of responsibility	
Exposure to violent media	
Association antisocial peers	

particularly important for the study of antisocial personality disorder. This model includes biological factors that in conjunction with social environment prepare a person to react aggressively in a certain situation. GAM also explains how multiple levels of the enumerated factors of aggression act on an individual through some social factors. However, the authors believe that all the responsibility is not, nor it can be in the social environment, which is often used as a justification of such behaviour, particularly in terms of violent and aggressive individuals who mostly believe that someone else is always responsible - bad society, violent video games or, for example, violence on TV (17, 18, 19). GAM model has a preventive character because it indicates risk factors, and prevention is always better than intervention, with a much greater chance of success if it is taken earlier (at a young age if possible).

Conclusion

The presence of aggressive and violent behaviour in patients with comorbidity of antisocial personality disorder and bipolar affective disorder could be observed at the right time and may be partially prevented by using General Aggressive Model. This model is significant because on the basis of the integrated model of aggression and multiple levels of the factors of aggressive behaviour it indicates the mode of action of risk factors not only for vulnerable groups, such as patients with comorbidity of these disorders, but also for mass population. Many patients with comorbidity of antisocial personality disorder and bipolar affective disorder have accepted aggression as a behavioural model from direct sources such as family, school, peers, as well as some indirect sources such as, for example, mass media, and this aggression is even upgraded with their personality pathology. A direct consequence of aggression as a model of behaviour, and not only as personality pathology, is an increased number of serious crimes which are committed by these patients.

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THE IMPORTANCE OF EARLY SUSPICION OF NON-MELANOCYTIC MALIGNANT SKIN CANCER (NMSC) IN PRIMARY AND SECONDARY HEALTH CARE

ZNAČAJ RANE SUMNJE NA NEMELANOCITNE MALIGNE TUMORE KOŽE (NMSC) U PRIMARNOJ I SEKUNDARNOJ ZDRAVSTVENOJ ZAŠTITI

Spomenka Paurević[1], Darko Lukić[2], Jozo Grgić[3], Nenad Babić[2], Duško Ivić[4], Predrag Lazić[5]

Summary

The prospective study, which took place from February 2011 to March 2014, included respondents who were sent for computerized dermoscopy because of non-melanocytic skin tumours. Respondents were divided into 2 groups. The first one, group A (45 respondents), consisted of respondents who had expressed concern about the observed changes in the skin and the desire for examination. The second one, group B (50 respondents) were respondents that did not come for examination due to changes on the skin, but for other reasons, so they had indirectly detected suspicious skin lesions.

The aim of this study is to analyse the importance of early suspicion of non-melanocytic malignant skin tumours by specialists in primary and secondary health care.

Parameters for comparison were respondents' subjective attitude of non-pigment skin lesions and dermoscopy and/or PH findings.

It has been shown that changes in the skin that bleed are sometimes highly suspect of NMSC because group A had 5 such cases and NMSC was detected in 4 cases, and group B had 7 respondents with haemorrhage and there were 4 with NMSC.

In group B, out of 12 respondents who said that they had found suspicious skin lesions caused by trauma, there were 8 NMSC, while in group A there were 3 cases, which is a statistically significant difference. In group B, out of 16 respondents who claimed that they had had suspicious skin changes dormant for years, NMSC has been proven in 3 cases, and in group A there was not NMSC which is also a statistically significant difference.

It was confirmed that the claims of the respondents are unreliable and that all patients should be addressed to computer dermoscopy, in patients with visible changes that arise even a slightest suspicion of NMSC.

Keywords: skin, cancer, dermoscopy.

Sažetak

Prospektivnom studijom, koja je trajala od februara 2011.godine do marta 2014. godine, obuhvaćeni su ispitanici koji su upućeni na kompjutersku dermoskopiju radi nemelanocitnih tumora kože. Ispitanici su podijeljeni u 2 grupe. Prvu, grupu A (45 ispitanika), činili su ispitanici koji su sami izrazili zabrinutost zbog uočene promjene na koži i želju za pregledom. Drugu, grupu B (50 ispitanika), činili su ispitanici koji nisu došli radi promjena na koži, nego iz drugih razloga, ali su im posredno uočene sumnjive kožne lezije.

Cilj rada je analiza značaja rane sumnje na nemelanocitne maligne kožne tumore od strane specijalista primarne i sekundarne zdravstvene zaštite.

Parametri za poređenje bili su subjektivni stav ispitanika o nepigmentnim lezijama kože i dermoskopski i/ili PH nalaz.

Dokazano je da su promjene na koži koje povremeno krvare visoko suspektne na NMSC jer je u grupi A od 5 takvih slučajeva NMSC su dokazani u 4 slučaja, a u grupi B od 7 ispitanika sa krvarenjem kod 4 se radilo o NMSC.

U grupi B od 12 ispitanika koji su iznijeli tvrdnju da su im sumnjive kožne promjene posljedica traume dokazano je 8 NMSC a u grupi A u 3 slučaja što je statistički značajna razlika. U grupi B od 16 ispitanika koji su iznijeli tvrdnju da im sumnjive kožne promjene godinama miruju dokazano je 3 NMSC a u grupi A nije bilo NMSC što je takođe statistički značajna razlika.

Potvrđeno je da su tvrdnje ispitanika nepouzdane te da na kompjutersku dermoskopiju treba uputiti sve pacijente kod kojih postoje vidljive promjene koje pobuđuju i najmanju sumnju na NMSC.

Ključne reči: koža, karcinom, dermoskopija

Introduction

All skin cancers, except for melanoma, are referred to as non-melanoma skin cancers (NMSC). The two most common non-melanoma skin cancers (NMSC) are the basal cell cancer (BCC) and squamous cell cancer (PCC). Both types of cancer occur more frequently in males. NMSC appears most frequently in adults, but can be seen in children as well (1).

BCC is the most common cancer in human population. The incidence of BCC in Europe is 100 per 100,000 inhabitants and in Australia it is 900 per 100,000 inhabitants (1).

BCC and PCC make up about 95% of all skin cancers, whereas melanoma makes about 4% and 1% are other rare skin cancers. The number of NMSC is increasing. In the USA in 2010 there were diagnosed 3.5 million diagnosed with NMSC per 2,000,000 patients (2).

The most important carcinogen for the skin is ultraviolet radiation, which causes DNA mutations, alteration of the genome and the uncontrolled growth of cancer cells. About 80% of skin cancer (except for melanoma) is formed on the skin exposed to the sun, and around 30% of NMSC occurs in the region around nose (3).

NMSC grow slowly and develop over the years. Since NMSC usually appears on face and scalp, it is very important during the treatment to take care of the functional and later aesthetic result. Of course, the basic principle of treating of NMSC should never be neglected - timely radical cancer removal.

Clinical diagnosis of pigmented skin lesions and non-pigmented is not often correct (3–6). In cases when NMSC is suspected, it is wise to examine the suspicious lesion by using computer dermoscopy. The accuracy of digital computer dermoscopy, in relation to the pH analysis, is from 98 to 100% (6).

Dermoscopy is now widely used in the EU, the USA and Australia. It is non-invasive, painless and bloodless, a superficial contact of microscope, with "in vivo" visualization of structure in epidermis and dermis, i.e. detection of changes that are not visible to the inspection review, scrutiny or human eye. This diagnosis does not imply any harmful effects and can be repeated indefinitely, regardless of the patient's age (4).

Aim of the study

The aim of this study is analysing the importance of early suspicion of non-melanocytic malignant skin tumours (NMSC) by specialists in primary and secondary health care.

Respondents and methods

The prospective study, which lasted from February 2011 to March 2014, included respondents who were referred to computerized dermoscopy because of non-melanocytic skin tumours. The respondents were divided into 2 groups.

The first one, group A (45 respondents), consisted of respondents who had expressed concern about the observed changes on the skin and had desire to be examined.

The second one, group B (50 respondents), contained the respondents that had not come for examination due to changes on the skin, but for other reasons, but suspicious skin lesions were indirectly detected.

For arriving at diagnosis the following were used: anamnesis, clinical examination and computerized dermoscopy, and definitive PH analysis after excision. Parameters for comparison were the subjective attitude of respondents about non-pigment skin lesions and dermoscopy and / or PH findings.

The observed parameters during the analysis were the following: gender, age, anatomical position of cutaneous tumours, as shown in Tables 1-3.

Table 1. Gender of respondents

Gender of respondents	Group A	Group B
Male	16(35,5 %)	32(64%)
Female	29(64,5%)	18(36%)
Total	45(100%)	50(100%)

Table 2. Age of respondents

Age of respondents	Group A	Group B
20-30	8(17,7 %)	9(18 %)
30-40	7(15,6 %)	9(18 %)
40-50	8(17,7 %)	13(26 %)
50-60	12(26,6 %)	8(16 %)
Over 60	10(22,3 %)	11 (22 %)
Total	45(100%)	50(100%)

Table 3. Location of tumour

Location of tumour	Group A	Group B
Forehead	3(6,6 %)	4(8 %)
Face (cheeks)	8(17,7 %)	10(20 %)
Nose	5(11,2 %)	8(16 %)
Earlobes	4(8,8 %)	3(6 %)
Upper eyelids	1(2,3 %)	3(6 %)
Lower eyelids	4(8,8 %)	2(4 %)
Scalp	7(15,6 %)	5(10 %)
Neck	4(8,8 %)	4(8 %)
Upper extremity	2(4,9 %)	1(2 %)
Lower extremity	1(2,3 %)	0(0 %)
Back	3(6,7 %)	5(10 %)
Chest	3(6,7 %)	5(10 %)
Total	45(100%)	50(100%)

Results

The research results are shown in Tables 4 and 5 and Figures 1 and 2. The parameters for comparison were

the following: subjective attitude to non-pigment skin lesions and dermoscopic and / or PH findings.

Table 4. Respondents' attitude to non-pigment skin changes and the reason of (not) coming for examination

Respondents' attitudes to non-pigment skin changes and the reason of (not) coming for examination	Group A	Group B
There are fears of non-pigment skin change	15 (33,3 %)	4(8 %)
The change is the result of hitting - trauma	3(6,7 %) (*3)	12(24 %) (*8)
Change occasional bleeding	5(11,2 %) (*4)	7(14 %) (*4)
The change is the same for several years	6(13,4 %)	16(32 %) (*3)
The change increases	12(26,6 %) (*1)	8(16 %) (*1)
Aesthetic problem	4(8,8 %)	3(6 %)
Total	45(100%)	50(100%)

*= NMCS

Figure 1. Attitude of respondents about non-pigment skin change and the reason of (not) coming for examination

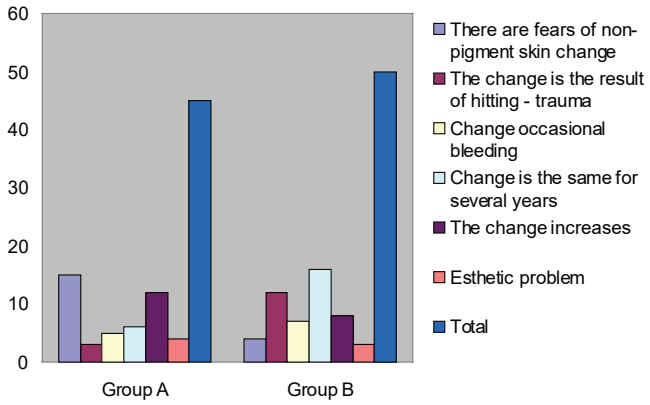
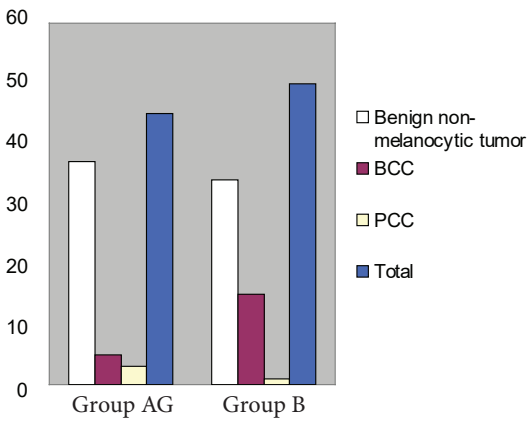


Table 5. Dermoscopic and / or PH findings

Dermoscopic and /or PH findings	Group A	Group B
Benign non-melanocytic tumour	37(82,1 %)	34(68 %)
BCC	5(11,2 %)	15(30 %)
PCC	3(6,7 %)	1(2 %)
Total	45(100%)	50(100%)

Figure 2. Dermoscopic and /or PH findings



By statistical analysis between the observed groups A and B, the following was ascertained:

- In terms of the characteristics of *respondents' attitude -fear of non-pigmented skin changes*, there is a statistically significant difference (p <0.01, reliability 99%), Z = 2. 293478
- In terms of the characteristics *of respondents' attitude- the change is the result of hitting (trauma)* there is a statistically significant difference (p <0.01, reliability 99%), Z = 2.86201
- In terms of the characteristics *of respondents' attitude - change is the same for several years*, there is a statistically significant difference (p <0.01, reliability 99%), Z = 2.764289
- In terms of the characteristics *of BCC skin PH finding* there is a statistically significant difference (p <0.01, reliability 99%), Z = 2.452421

Discussion

The analysis included 95 subjects, 48 males and 47 females. In group A women are almost twice more likely to come to the examination then men. This can be explained as a higher concern of the female population with changes on the skin. On the contrary, in group B male respondents are twice more likely to have had a legitimate reason for dermoscopic examination. This at the same time showed that women are more responsive to changes on the skin, and that suspicious changes more often appear on male skin.

NMSC are usually positioned on body parts that are most exposed to the sun. The skin that has been damaged by UV rays with the visible solar spots and actinic keratosis is predilective place for NMSC (4-7). Dominant anatomical region where NMSC was registered in our respondents is the head (scalp, face, nose), which is consistent with the data from literature.

Skin examination was often required by patients who had a completely irrational fear of skin tumour (8).

In group A, 15 respondents came for examination because of irrational, general fear of skin lesions and desire to check it. In group B only 4 respondents had the attitude of fear of non-pigmented skin changes, which proved to be statistically significantly different. However, in Group A out of 15 respondents who came for examination only due to irrational fear of existing skin lesions, NMSC was not detected in any of those cases.

A large number of individuals with obvious changes on the skin ignore them or deny the disease, explaining skin lesions to be the result of injury or some other trivial coincidence (4).

In group B, the dominant respondent's attitude was that their non-pigmented tumorous lesions were caused by trauma. Namely, there were significantly different efforts among respondents from group B compared to those from group A, to attribute the formation of skin lesions to previous violation and not to disease and tumour hearth. This attitude can be explained as subjective rationalization and escape from the fact that there is a skin tumour. At the same time, among 12 patients from group B, who alleged changes to violation of the skin, NMCS was found in 8 (66,6%).

One respondent from group B who was recommended dermoscopy due to changes on the nose, and suspicion of BCC, resisted having dermoscopic examination for a long time, as well as operation itself. He insisted that the change on the nose was not a tumour but the consequence of frequent injuries during washing his face, because his fingers were bent due to Dupuytren's contracture. Dermoscopy and PH findings confirmed BCC.

Basal cell carcinoma (BCC) is the most commonly occurring NMSC, it appears first on the head, especially on the face and rarely on the palms or feet. BCC is primarily described as a small, inconspicuous, irregular, reddish change that can create discrete ulceration. The lesion bleeds occasionally as tumour progresses. Slow tumour development can be visible for many years (4-9).

Transient slight bleeding from the skin non-melanocytic lesion proved to be a significant priority for early suspicion of NMSC in our respondents. Out of 5 patients with occasional bleeding from skin lesions in group A NMSC were confirmed in 4 (80%) of them. In group B, out of 7 patients with the same symptoms, NMSC was also found in 4 (57,1%) of them.

NMSC often begins as a seemingly harmless erosion of the epidermis, or as a small sore that takes long to heal. It usually heals by forming scabs, which spontaneously fall off, but leaves a vulnerable area. Eventually, the vulnerable area increases and becomes irregularly edged. This genesis changes deceive many patients (7).

In some cases, NMSC, especially BCC, can give the appearance of a fully rehabilitated incrusted skin changes (9). That is the reason why a larger number of lay people do not think it is a dangerous cutaneous lesion. Such changes may be misleading to clinicians as well (10).

In our respondents from group B, 16 of them (32%) had the current change on the skin considered harmless, primarily because it "suspended" for years. It has been shown that among these lesions there were 3 (18,7%) NMSC. In group A, 6 (13,3%) respondents reported a long time non-pigmented, motionless skin changes but it turned out that among them there were not NMSC. By this characteristic was observed as a significant difference.

Most NMSC have a limited potential for growth, but they can be very aggressive and then reach a considerable size and penetrate deeply. On the face they can ruin eyes and nose or penetrate through the skull and attack meninges. In this form NMSC is fatal (11).

Therefore, the early suspicion of NMSC is crucial. Quick diagnosis allows timely and optimal radical surgery by which the local tumour is removed in its entirety and the aesthetic appearance of the patient are in the area of disfigurement. In our respondents in both groups very aggressive NMSC were not found.

In our respondents in group A, NMSC was diagnosed in the total of 8 (17,8%) respondents, and in group B in 16 (32%) respondents. At the same time, significant statistical difference was observed in terms of the incidence of basal cell cancer (BCC) because it was proven three times more common in the patients from group B.

Various studies have established certain parameters and risk factors that lead to the progression and dissemination of NMSC. These are macroscopic parameters (size, shape and multifocality of tumours) and the microscopic parameters (degree of cell differentiation) (12).

Generally, NMSC is not characterized by aggressive mood with a rapid formation of metastases. Cancers that occur on sun-damaged skin, have a very low susceptibility to metastasis, with the incidence of approximately 0.5% (11). On the contrary, NMSC incurred after inflammation and degenerative processes have a much higher degree of metastasising than those which develop on sun-damaged skin (13).

During our analysis there were no verified cases of disseminated forms of NMSC.

Conclusion

It has been shown that changes on the skin that sometimes bleed are highly suspicious of NMSC because in group A NMSC were detected in 4 out of cases, and in group B NMSC was discovered in 4 out of 7 respondents with haemorrhage.

In group B NMSC was proven in 8 out of 12 respondents who presented with the claim that their suspicious skin lesions were caused by trauma, and in group A in there were 3 cases, which is a statistically significant difference. In group B NMSC was proven in 3 out of 16 respondents who presented with a claim that their suspicious skin changes were dormant for years, whereas in group A there were no NMSC, which is also a statistically significant difference.

It was confirmed that the claims of respondents were unreliable and that all patients should be referred to the computer dermoscopy if there are visible changes that give rise to the slightest suspicion of NMSC.

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THE IMPORTANCE OF EARLY SUSPICION OF MELANOMA IN PRIMARY AND SECONDARY HEALTH CARE

ZNAČAJ RANE SUMNJE NA MELANOM U PRIMARNOJ I SEKUNDARNOJ ZDRAVSTVENOJ ZAŠTITI

Spomenka Paurević[1], Darko Lukić[2], Jozo Grgić[3], Nenad Babić[2], Duško Ivić[4], Predrag Lazić[5]

Summary

The prospective study, which lasted from February 2011 to March 2014, included respondents who were referred to computerized dermoscopy due to melanocytic skin tumours. The respondents were divided into 2 groups. The first one, group A, (38 respondents) consisted of respondents who had personally expressed concern about the existing pigment changes on the skin and had desire for examination. The second one, group B, (40 respondents) consisted of respondents that did not come for examination due to changes on the skin, but for other reasons, but suspicious skin lesions were indirectly detected.

The aim of this study was to analyse the importance of early suspicion of melanocytic malignant skin tumours by specialists of primary and secondary health care

Parameters for comparing the results were respondents' subjective attitude to pigmented skin changes, as well as dermoscopy and / or PH finding.

There was no statistically significant difference between groups in terms of respondents' attitudes to pigmented skin lesions, i.e. fear of skin changes, the belief that moles should not be touched (operated on), or that pigment changes that they have since birth are not dangerous.

Early suspicion of melanoma in Group B resulted in detection of 4 nodular melanoma and 3 superficial spreading melanoma, while in group A there were no malignant skin lesions, which is a statistically highly significant difference.

It was confirmed that early suspected melanoma and referring patients to dermoscopic examination had advantages as working principle in any clinic or any specialty.

Keywords: skin, melanoma, dermoscopy.

Sažetak

Prospektivnom studijom, koja je trajala od februara 2011. godine do marta 2014. godine, obuhvaćeni su ispitanici koji su upućeni na kompjutersku dermoskopiju radi melanocitnih tumora kože. Ispitanici su podijeljeni u 2 grupe. Prvu, grupu A (38 ispitanika), činili su ispitanici koji su sami izrazili zabrinutost zbog postojeće pigmentne promjene na koži i želju za pregledom. Drugu, grupu B (40 ispitanika), činili su ispitanici koji nisu došli radi promjena na koži, nego iz drugih razloga, ali su im posredno uočene sumnjive kožne lezije.

Cilj rada je analiza značaja rane sumnje na melanocitne maligne kožne tumore od strane specijalista primarne i sekundarne zdravstvene zaštite.

Parametri za poređenje rezultata bili su subjektivni stav ispitanika prema pigmentnim kožnim promjenama, kao i dermoskopski i/ili PH nalaz.

Nije pronađena statistički značajna razlika među grupama u pogledu odnosa ispitanika prema pigmentnim lezijama kože, tj. straha od kožnih promjena, vjerovanja da mladeže na koži ne treba dirati (operisati), kao i da pigmentne promjene koje postoji od rođenja nisu opasne.

Rana sumnja na melanom u grupi B rezultirala je otkrivanjem 4 nodularna melanoma i 3 površno šireća melanoma dok u grupi A nije bilo malignih lezija kože, što je statistički visoko značajno različito.

Potvrđeno je da rana sumnja na melanom i upućivanje pacijenta na dermoskopski pregled imaju prednost kao princip rada u svakoj ambulanti bilo koje specijalnosti.

Ključne reči: koža, melanom, dermoskopija

Introduction

Describing melanoma in 1787, John Hunter said it was "a small cancer, which requires major surgery". He described metastatic infiltration of melanoma in lymphatics below the mandible in a man aged 35. He removed the tumour mass and after 3 years there was a relapse (1).

In 1838, Norris quite rightly described melanoma as a skin change, mostly black, but more often polychrome, with asymmetrical edges, sometimes with local satellites. Then he concluded that more often people with fair skin and with freckles get it and warned of a relationship between moles and melanoma, as well as of a particular family predisposition. He concluded that melanoma was very prone to spread to visceral organs and that in case of late diagnosis, in the stage of disseminated disease, there was no effective therapy (1).

Melanomas are tumours whose behaviour is most difficult to predict (2). It can often 'stagnate' for many years (2, 3). Some of them are highly malignant with the worst

prognosis, while others, although with a similar histology, can be relatively benign (3, 4).

Today, the dominant opinion is that melanoma arises from moles (5). This specially refers to younger patients or patients whose pigment change takes less time. Others believe that the incidence of melanoma on the intact skin is very similar to the incidence of melanoma that is thought to have arisen from benign skin pigmentation.

Congenital melanocytic changes or those that are remembered from childhood are more often the place where malignant alteration remains overlooked for a longer period of time. Changes that have occurred "de novo" draw more attention to themselves (6).

The incidence of melanoma increases every year. For the past 45 years, according to the data from the Scandinavian countries, America and Australia, the incidence of melanoma is higher than incidence of any other malignant tumour (7, 8). In our country there is no accurate statistics on the incidence of the disease.

Timely, accurate diagnosis is the only chance for curing melanoma. Clinical evaluation of malignant pigmented lesions as benign mislead the patient who loses valuable time and the chance for cure (9).

Although melanoma can be non-melanotic, the most common diagnostic problem is distinguishing harmless moles from melanoma (5, 6). In all cases, when there's a doubt about the character of pigmented skin lesions, computer (digital) dermoscopy is available now, as in-vivo diagnostics choice.

Aim of the study

The aim of this study was to analyse the importance of early suspicion on melanocytic malignant skin tumours by specialists of primary and secondary health care.

Respondents and methods

The prospective study, which lasted from February 2011 to March 2014, included respondents who were referred for computerized dermoscopy due to melanocytic skin tumours. The respondents were divided into 2 groups.

The first one, group A (38 respondents), consisted of respondents who themselves had expressed concern about the existing pigment changes on the skin and had desire for examination.

The second one, group B (40 respondents), consisted of respondents that had not come for examination due to changes on the skin, but for other reasons, but they were indirectly detected suspicious skin lesions.

The observed parameters during the analysis were the following: gender, age, and skin lesions whose anatomical positions were as shown in Tables 1-3.

All respondents had computer dermoscopy of skin done, in order to determine the character of skin lesions in vivo, prior to surgery.

Table 1. Distribution of respondents by gender

Gender	Group A	Group B
Male	20(52,6 %)	17(42,5 %)
Female	18(47,4 %)	23(57,5 %)
Total	38 (100%)	40(100%)

Table 2. distribution of respondents by age

Age	Group A	Group B
10-20	2 (5,3%)	3(7,5%)
20-30	2(5,3%)	1(2,5%)
30-40	8(21,1%)	9(22,5%)
40-50	10(26,3%)	8(20%)
50-60	10(26,3%)	11(27.5%)
Over 60	6(15,7%)	8(20%)
Total	38 (100%)	40(100%)

Table 3. Distribution of respondents by anatomic position of pigmented lesions

Anatomic position	Group A	Group B
Head and neck	5(13,2%)	8(20%)
Upper extremity	4(10,5%)	2(5%)
Lower extremity	6(15,7%)	0(0%)
Chest	9(23,7%)	9(22,5%)
Back	9(23,7%)	15(37,5%)
Stomach	4(10,5%)	6(15%)
Genitals	1(2,7%)	0(0%)
Total	38 (100%)	40(100%)

Table 4. Relation to pigmented skin tumours

Relation to pigmented skin changes	Group A		Group B	
	Yes	No	Yes	No
Fear of skin changes	30(78,9%)	8(21,1%)	27(67,5%)	13(32,5%)
Mole that exist from birth is not dangerous	28(73,7%)	10(26,3%)	33(82,5%)	7(17,5%)
Skin changes should not be operated	28(73,7%)	10(26,3%)	36(90%)	4(10%)
Total	38 (100%)		40(100%)	

Results

The results of the analysis in the studied groups are shown in Tables 4-6 and Figures 1 and 2. Parameters for comparing results were subjective attitude of respondents related to the pigmented skin changes: fear of skin changes, prejudices like "moles on the skin should not be operated on, moles that exist since birth are not dangerous", as well as inspection, dermoscopy and / or PH finding.

Table 5. Clinical findings and the reason for referring the patient at dermoscopy

Clinical findings and the reason for referring the patient at dermoscopy	Group A	Group B
Efelid and other hyperpigmentation	2(5,3%)	1(2,5%)
Lesions suspected as superficial spread of melanoma	3(7,8%)	10(25%)
Nevus	32(84,2%)	21(52,5%)
Lesions suspected as nodular melanoma	1(2,7%)	8(20%)
Total	38 (100%)	40(100%)

Figure 1. Clinical findings and reason for referring the patient to dermoscopy

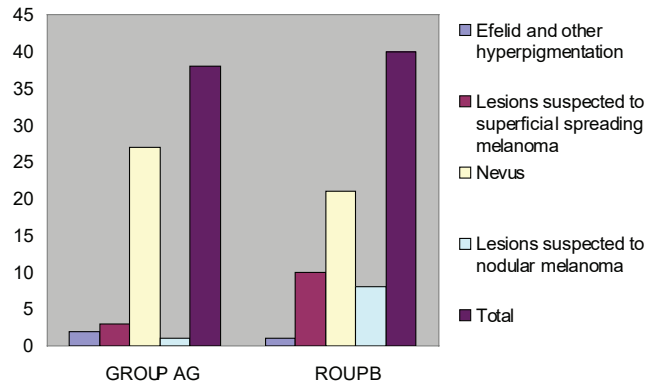
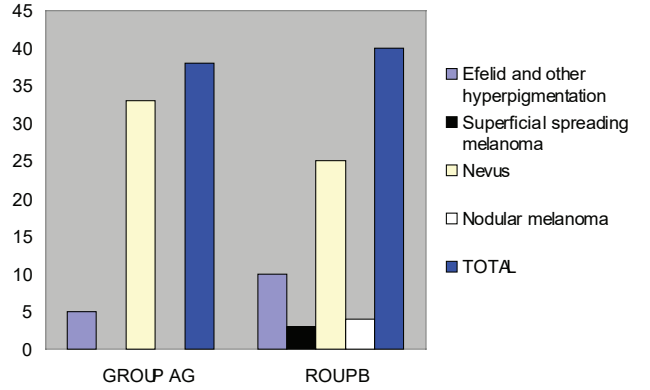


Table 6. Dermoscopic and PH findings

Dermoscopic and PH findings	Group A	Group B
Efelid and other hyperpigmentation	5(13,2%)	10(%)
Superficially spreading melanoma	0(0%)	3(%)
Nevus	33(86,8%)	25(%)
Nodular melanoma	0(%)	4(%)
Total	38 (100%)	40(100%)

Figure 2. Dermoscopic and PH findings



In statistical analysis between the observed groups A and B the following was ascertained::

There is no statistically significant difference, with the characteristics of *the relation to the pigmented skin changes-fear of pigmented skin changes* (p> 0.01).

There is no high statistically significant difference, with the characteristics *of relation to pigmented skin changes - "changes should not be operated on"* (p> 0.01),

There is no high statistically significant difference, with the characteristics *of relation to pigmented skin changes - "a change since birth is not dangerous"* (p> 0.01),

There is a highly significant difference in the characteristics of *the reason for refer a pigment changes to dermoscopy- pigment changes suspected to superficially spreading melanoma*, p <0.01, (reliability 99%), Z = 2.092780

There is highly significant difference in the characteristics *of the reason for referring a pigment change to dermoscopy - pigment changes suspected to nodular melanoma* p <0.01, (reliability 99%), Z = 3.027764

There are highly significant difference in the characteristics of *dermoscopy and pH findings- superficially spreading melanoma,* p <0.01, (reliability 99%), Z = 2. 542913

There is highly significant difference in the characteristics of *dermoscopy and PH finding - nodular melanoma* p <0.01,(reliability 99%), Z = 2.875152

Discussion

37 out of 78 respondents (47,4%) were male and 41 (52,6%) were female. The youngest respondent was 11 years old.

There are many reasons why patients are reluctant to come for examination of the skin and are late with timely diagnosis of melanoma. As skin tumours are clearly visible, delayed diagnosis is primarily the result of prejudice, lack of information and ignorance (10).

The belief of lay people that "moles should not be touched" is certainly one of the main prejudices when we talk about skin tumours. Moles certainly should not be irritated, but they need to be controlled and removed at slightest suspicion (10).

Today it is known that if a child was born with large or gigantic nevi, there is a greater risk of developing melanoma on such lesion (11). The fact that the pigment changes on the skin are congenital is not a quart of possible evolution in malignant tumour (12).

Within the analysed attitude of our respondents about pigmented skin changes, it was shown that both groups have almost the same opinion about it. Namely, in both groups (ir)rational fear of pigmented skin tumours prevail, i.e., pigmented skin lesions are considered as dangerous themselves. At the same time, both groups believe that it is dangerous to remove pigment changes on the skin. Both groups believe that the inherent pigmented changes are usually harmless.

Recent researches have shown that there is virtually no anatomical region that is "safe" from melanoma, regardless covered or not covered regions of the body (7). This fact has been also confirmed by our research.

Melanoma can occur by alteration from moles or to previously intact skin (6). In any case, timely diagnosis is invaluable (9). This tumour may be innate and inactive for a long time and give opportunity for timely diagnosis (12). In the phase "in situ", when skin melanoma is thinner than 1 mm, there is a possibility to cure this disease (13).

Although melanoma is often an obvious skin change, it often happens that the diagnosis is delayed. Patients usually come for examination when skin changes definitely arouse their concern, as they either bleed or rapidly change shape or colour (6).

Burdened by mentioned prejudices about pigmented skin changes, respondents from group A the most frequently came for examination when they noticed an obvious change of skin lesions (variations in shape, diameter or colour) which caused their concern. Respondents in group B basically ignored these changes.

In the diagnosis of melanoma, nevi cause the biggest trouble, as they macroscopically resemble melanoma. Problematic lesions mainly belong to the group of melanocytic dysplasia (6, 10). Clinical diagnosis in our respondents from groups A and B proved to be true in most cases, i.e. in group A in 100% of cases, and in group B in 97% of cases.

The clinical diagnosis of melanoma is often unreliable, but suspicion itself of initial melanoma is very much appreciated (9, 10). When it turns out that the suspicion was not justified, the patient will not have any damage. On the contrary, when it is shown that the early suspicion of melanoma during the second examination was justified, patient's life will be saved (10, 11).

Therefore, the first step, in cases of suspected melanoma in our respondents, was sending them to have computer dermoscopy done.

Suspicion of superficial spreading melanoma in our respondents in group A was observed in 3 cases and in all the cases, fortunately it was false. In group B the superficial spreading melanoma raised suspicion in 10 respondents of whom in 3 (33%) cases the doubt was justified. There is statistically significant difference according to the number of detected superficial spreading melanoma between groups A and B.

Suspicion of nodular melanoma, in our respondents in group A, was observed in 1 case and it was false. In group B, the nodular melanoma was suspected in 8 respondents, of whom at 4 (%) doubts were justified. Thus, statistically significant difference was noticed according to the number of detected melanoma between groups A and B .

The absence of melanoma in group A can be explained by the fact that in this group the dominant respondents that are psychologically vulnerable to skin changes or they perceive that seriously and responsibly, although they are sometimes phobic, so they often required review of quite benign pigmented lesions.

On the contrary, the fact that melanomas were detected only in group B, explains the technology by which the slightest suspicion of melanoma (at patients were reviewed for another reason and skin lesions were detected indirectly), was checked by referring them to computer dermoscopy.

Computer (digital) dermoscopy correlated with PH analysis of 98-100%, so it is extremely important that suspicious skin changes are referred to the in vivo diagnosis. Dermascopic diagnostics is available for determination of the character of skin lesions, prior to surgery (14, 15). Thus, it is possible to assess the need for optimal radical surgical treatment in the first surgical operation, and not after a questionable clinical diagnosis, or PH analysis after primary surgery (16).

Conclusion

It has not been found statistically significant difference between the groups in terms of the relation of respondents to skin pigmented lesions, i.e. fear of skin lesions, the belief that the moles should not be touched (operated on), as well as that pigment changes that exist since birth are not dangerous.

Early suspicion of melanoma in Group B resulted in detection of 4 nodular melanoma and 3 superficial spreading melanoma, while in group A there were no malignant skin lesions, which is statistically highly significant difference.

It was confirmed that the early suspicion of melanoma and referring patients to dermoscopic examination have the advantage as principle of work in any clinic of any specialty.

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ROLE OF MAGNESIUM

ULOGA MAGNEZIJUMA

Nikolina Banjanin[1]

Summary

The role of magnesium is investigated in many studies. The results of investigations showed different mechanisms of action of magnesium. Magnesium intake may be from food, water and supplements. Results of studies showed that magnesium has effect on postoperative pain, coronary arteries calcification, body mass index, cardiovascular diseases, incidence of colorectal cancer.

Keywords: magnesium, role

Sažetak

Uloga magnezijuma istraživana je u mnogim studijama. Rezultati istraživanja pokazali su različite mehanizme dejstva magnezijuma. Magnezijum je moguće uneti hranom, vodom i suplementima. Rezultati studija pokazali su da magnezijum ima efekat na postoperativni bol, kalcifikaciju koronarnih arterija, indeks telesne mase, kardiovaskularne bolesti, incidenciju kolorektalnog karcinoma.

Ključne reči: magnezijum, uloga

Uvod

Mnoge studije različitih dizajna bavile su se istraživanjem uloge magnezijuma. Rezultati istraživanja pokazali su različita dejstva magnezijuma.

Pokazano je da je prisustvo jona magnezijuma potrebno za aktivnost ATP-aze (1). Navodi se da ordiniranje magnezijuma tokom opšte anestezije smanjuje postoperativni bol, pri čemu ne dovodi do povećanja neželjenih efekata (2). Studija je pokazala da je visok unos magnezijuma inverzno povezan sa koncentracijama pojedinih markera sistemske inflamacije i endotelne disfunkcije (3). Istraživanje koje je sprovedeno u Koreji uočilo je povezanost između niske koncentracije serumskog magnezijuma i kalcifikacije koronarnih arterija (4). Nađena je i negativna korelacija između koncentracije magnezijuma u serumu i krvnog pritiska, indeksa telesne mase, odnosa kuk-struk i obima struka (5).

Unos magnezijuma u organizam

Magnezijum je moguće uneti u organizam hranom, vodom i suplemetima. Prema Recommended Dietary Allowance preporučeni nivo dnevnog unosa magnezijuma za muškarce iznosi 400 mg (uzrasta od 19 do 30 godina) i 420 mg (za starije od 31 godine), a za žene 310 mg (19-30 godina) i 320 mg (preko 31 godine) (6). Kada su u pitanju dijetetski suplementi, prema pravilniku o zdravstvenoj ispravnosti dijetetskih proizvoda dodaci ishrani (dijetetski suplementi) su namirnice koje dopunjuju normalnu ishranu i predstavljaju koncentrovane izvore vitamina, minerala ili drugih supstanci sa hranjivim ili fiziološkim efektom, pojedinačno ili u kombinaciji, a u prometu su u doziranim oblicima dizajnirane da se uzimaju u odmerenim pojedinačnim količinama (kapsule, tablete, kesice praška, ampule tečnosti, bočice za doziranje u kapima i dr.) (7). Jedna studija je ispitivala povezanost unosa magnezijuma hranom i suplementima sa incidencijom kolorektalnog karcinoma. Pokazano je da je unos magnezijuma oko 400 mg/dan hranom i suplementima povezan sa nižom incidencijom kolorektalnog karcinoma (8).

Uloga magnezijuma u kardiovaskularnim bolestima

Velika pažnja posvećena je i istraživanju uloge magnezijuma u kardiovaskularnim bolestima. Naime, studija sprovedena u Švedskoj pokazala je da je umiranje od akutnog infarkta miokarda u negativnoj korelaciji sa koncentracijom magnezijuma u vodi za piće (9). Ispitivana je i povezanost magnezijuma u serumu sa kardiovaskularnim mortalitetom. Uočeno je da je niska koncentracija magnezijuma u serumu povezana sa većim kardiovaskularnim mortalitetom (10).

Hipertenzija predstavlja značajan javnozdravstveni problem današnjice. Prema podacima Svetske zdravstvene organizacije 2008. godine prevalencija povišenog krvnog pritiska kod odraslog stanovništva uzrasta 25 godina i više iznosila je oko 40 % (11). Prema podacima iz 2006. godine prevalencija povišenog krvnog pritiska u Srbiji kod odraslog stanovništva iznosila je 46,5% (12). Studija sprovedena u Indiji pokazala je da su nivo serumskog magnezijuma i hipertenzija u negativnoj korelaciji (13). Istraživanje sprovedeno u Belgiji ustanovilo je negativnu povezanost između unosa magnezijuma hranom i sistolnog krvnog pritiska kod žena (14). Kada je reč o vodi za piće, studija sprovedena u Tajvanu uočila je da je nivo magnezijuma u vodi za piće inverzno povezan sa rizikom umiranja od hipertenzije (15).

Zaključak

Istraživanja pokazuju da je uloga magnezijuma važna. Naime, rezultati studija navode da magnezijum ima efekat na postoperativni bol, kalcifikaciju koronarnih arterija, indeks telesne mase, kardiovaskularne bolesti, incidenciju kolorektalnog karcinoma.

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