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AKUTNI MIKSEDEM NAKON TERAPIJE HIPERTIREOZE RADIOAKTIVNIM JODOM I POSLEDICE

Sažetak: Prikazujemo slučaj pacijentkinje kod koje je, nakon terapije Graves-ove hipertireoze radioaktivnim jodom, nastala teška, klinički manifestna hipotireoza u okviru koje je došlo do razvoja pretežno senzitivne neuropatije dominantno aksonalnog tipa. Pored simptoma i neurofizioloških znakova polineuropatije, kod pacijentkinje su se tokom 2 godine naizgled adekvatne monoterapije hipotireoze levotiroksinom održavali hipotireoidni simptomi od strane CNS-a, povišene serumske koncentracije ukupnog i LDL holesterola i klinički znakovi povećanog perifernog vaskularnog otpora. Održavao se nefiziološki odnos serumskih koncentracija FT3 i FT4, uz serumske koncentracije TSH i FT4 koje su ukazivale na smanjenu osetljivost tireoidno-hipofizne negativne povratne sprege.

Nakon započinjanja kombinovane LT4/LT3 supstitucione terapije veoma brzo je došlo do nestanka hipotireoidnih simptoma vezanih za CNS, značajnog smanjenja serumskih koncentracija ukupnog i LDL holesterola, normalizacije FT3/FT4 odnosa makar u prvim časovima nakon uzimanja leka, nestanka kliničkih znakova povećanog perifernog vaskularnog otpora. Stepen polineuropatskih tegoba se smanjio do nivoa kad ne ometa spavanje. Vreme i kontrolna ENG će pokazati kakvi će biti definitivni efekti kombinovane T4/T3 terapije na oštećenja perifernih nerava. Tokom prvih 6 meseci nisu zabeleženi neželjeni efekti kombinovane T4/T3 terapije.

Ključne reči: radioaktivni jod, hipertireoza, polineuropatija, hipotireoza, T4/T3 terapija

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Uvod

Terapija radioaktivnim jodom smatra se veoma pouzdanim i bezbednim postupkom kad je u pitanju trajno lečenje autoimune hipertireoze – Graves-ove bolesti. U SAD-u se često koristi i kao inicijalna terapija u lečenju ove bolesti. U stručnoj literaturi se naglašava da je jedina moguća komplikacija nastanak trajne hipotireoze, a mnogi čak smatraju da je rani nastanak hipotireoze željeni cilj terapije, s obzirom na to da je, dugoročno gledajući, gotovo nemoguće izbeći takav ishod, a hipotireozu je navodno veoma lako lečiti (1).

Prikaz slučaja

Prikazujemo slučaj pacijentkinje, stare 41 godinu, koja je lečena zbog Gravesove bolesti radioaktivnim jodom. Kod pacijentkinje je dijagnostifikovana hipertireoza u 28. godini života. Dugotrajno je lečena medikamentno propiltiouracilom. Nakon 6 godina terapije propiltiouracilom došlo je do remisije. Tri godine kasnije došlo je do recidiva. Sledeće 3 godine je ponovo lečena propiltiouracilom, a zatim je primenjena terapija radioaktivnim jodom u dozi od 11 mCi. Tri meseca nakon terapije pacijentkinja je u eutireoidnom stanju.Serumska koncentracija FT4 je 16,2 mmol/l, FT3 4,5mmol/l, TSH 0,4 ml U/l. Izuzetno je dobrog zdravstvenog stanja i bez bilo kakvih simptoma. Naredna kontrola je zakazana za tri meseca. Desetak dana kasnije pacijentkinja dobija egzacerbaciju hroničnog sinuzitisa i bez uspeha se leči nekoliko nedelja. U tom periodu javljaju se umor, malaksalost, neraspoloženje i promuklost. Sedam nedelja nakon prethodne kontrole, pacijentkinja primećuje naglo pogoršanje opšteg stanja, zamaranje i tahikardiju. Laboratorijske analize ukazuju na tešku hipotireozu: TSH je 60 ml U/l, a FT4 2,6 pmol/l. (Tabela1) Ubrzo nakon započinjanja supstitucione terapije levotiroksinom dolazi do razvoja neuroloških simptoma. Iznenadne simetrične parestezije u šakama bude pacijentkinju iz sna. Istovremeno se razvija permanentan osećaj zatezanja i pečenja prednjeg trbušnog zida. Pored toga, tokom naredna dva meseca izraženi su teški simptomi hipotireoze od strane svih organskih sistema. Česti napadi gušenja i tahikardija, sindrom apneje u snu, panični napadi u nekoliko navrata, promuklost, malaksalost, depresija, vrtoglavica, diskretna dizartrija, osećaj otežanog gutanja. EKG pokazuje mikrovoltažu, difuzno aplatirane i bifazne T talase uz lako proširen QRS kompeks. (Slika 1) Ehokardiografski nalaz je uredan. Laboratorijske analize ukazuju na povećane vrednosti CK i serumskog holesterola.

Nakon dostizanja laboratorijskog eutireoidnog stanja parestezije se generalizuju i postaju permanentne i postepeno dobijaju kvalitet neuropatskih bolova. Neurološki nalaz je uredan. Prvim ENG pregledom nisu verifikovani znakovi polineuropatije. Elektroforeza proteina seruma i urina pokazale su normalan nalaz. Imunofiksacija

proteina seruma i urina pokazuje uredan nalaz. HBs Ag i anti HCV antitela su negativna.

Imunološke analize pokazuju prisustvo p-ANCA autoantitela najpre u titru 1:80, zatim 1:20 i na kraju su negativna, anti MPO antitela su lako povišena –7,7 U/ml (normalno do 5U/ml). ANA antitela su negativna, a u jednom navratu su nađena lako povišena antiRo SSA antitela 56 U/ml (normalno do 25U/ml), ali nekoliko meseci kasnije nalaz je uredan – 5U/ml. Antiparijetalna, antiglijadinska i endomizijalna antitela su negativna. Krioglobulini su negativni. Serumski imunoglobulini su uredni. Imuni kompleksi nisu prisutni. Test opterećenja glukozom je uredan (Tabela 2).

Neurolog smatra da se radi o tireoidnoj polineuropatiji tankih vlakana i predlaže simptomatsku terapiju Lirica i Amitriptillin tbl, ali zbog neželjenih efekata i nedovoljne efikasnosti terapija je obustavljena nakon 4 nedelje.

Dve godine nakon terapije radioaktivnim jodom ENG nalaz ukazuje na postojanje više senzitivne, dominantno aksonalne neuropatije na tanjim nervima donjih i gornjih ekstremiteta (Tabela 3).

Uprkos supstitucionoj terapiji levotiroksinom u dozi od 125 mcg na dan i serumskoj koncentraciji TSH oko 1 mlU/l, neprekidno se održavaju malaksalost, smanjena koncentracija, zaboravnost, depresija i generalizovani neuropatski bolovi. Odnos serumskih koncentracija FT3/FT4 je snižen. Održavaju se i povišene serumske koncentracije ukupnog i LDL holesterola.

Ekspertsko mišljenje tireoidologa je da polineuropatija ne može biti u vezi s hipotireozom niti s terapijskim postupkom, i da je potrebno polineuropatiju lečiti pod kontrolom neurologa, a zbog depresivnih simptoma potrebno je lečenje od strane psihijatra.

Dve i po godine nakon nastanka hipotireoze uvedena je kombinovana supstituciona terapija L tiroksinom i L trijodtironinom i to 100 mcg L tiroksina i 10 mcg L trijodtironina, podeljeno u 2 dnevne doze. Veoma brzo dolazi do nestanka hipotireoidnih simptoma vezanih za CNS. Stepen polineuropatskih smetnji se tokom prvih šest meseci kombinovane terapije veoma postepeno smanjuje do nivoa kad uglavnom ne ometa spavanje. Pored toga, pacijentkinja primećuje da ponovo ima tople šake, za razliku od prethodne dve zime tokom kojih je bila na monoterapiji L tiroksinom. Dolazi i do normalizacije odnosa serumskih koncentracija FT3/FT4, makar u prvim časovima nakon uzimanja leka. (Tabela 5) Serumske koncentracije TSH su približno iste tokom monoterapije L tiroksinom 125 mcg/ dan i kombinovane T4/T3 terapije (Tabela 4 i 5).

Diskusija

Povezanost između polineuropatije i hipotireoze nije široko poznata među endokrinolozima. Na internetu čak postoji sajt na kojem su se okupili pacijenti koji se

žale da njihovi endokrinolozi ne uviđaju vezu između hipotireoze i polineuropatije. (1) Međutim, o tom problemu postoji značajna naučna literatura. Senzitivna polineuropatija se javlja u nelečenoj, ali i lečenoj kliničkoj, pa čak i supkliničkoj hipotireozi, bez obzira na uzrok hipotireoze (3), (4), (6), (7), (8), (9), (10), (11).

Ettore Beghi i saradnici pronašli su među 39 pacijenata s primarnom hipotireozom različitog uzroka, trajanja i nezavisno od toga da li je započeto lečenje ili ne, subjektivne polineuropatske smetnje u 64% pacijenata, a elektroneurografska dijagnoza polineuropatije postavljena je u 72% slučajeva (3).

Flavia Magri i saradnici su pronašli smanjenu gustinu intraepidermalnih nervnih vlakana u 60% pacijenata sa nelečenom kliničkom hipotireozom i kod 25% pacijenata sa nelečenom supkliničkom hipotireozom (4), i dokumentovali su povećanje gustine intraepidermalnih nervnih vlakana kod tih pacijenata nakon terapije L tiroksinom (5).

Kristin Orstavik i saradnici zaključili su da neki pacijenti s lečenom hipotireozom imaju simptome neuropatije tankih vlakana (6).

Penza P. i saradnici opisuju slučaj pacijentkinje kod koje su simptomi polineuropatije tankih vlakana bili prvi znak supkliničke hipotireoze. Nakon supstitucione terapije levotiroksinom došlo je do potpunog kliničkog i neuropatološkog oporavka (7).

Fabio Monzani i saradnici utvrdili su veliku učestalost neuromišićnih simptoma kod pacijenata koji imaju supkliničku hipotireozu i oporavak nakon uvođenja supstitucione terapije L tiroksinom (8).

D.J. Dick i saradnici opisuju slučaj pacijenta sa senzitivnom neuropatijom kao jedinim simptomom teške hipotireoze. Nakon supstitucione terapije tiroksinom dolazi do potpunog kliničkog i ENG oporavka (9).

Prema tome, senzitivna polineuropatija može biti uzrokovana hipotireozom. O njoj se malo misli zato što je veoma često blaga, pa pacijenti i ne spominju simptome, a često je i supklinička (4). Kod nekih pacijenata subjektivni simptomi i objektivni znakovi (patološki nalaz ENG i smanjena gustina perifernih nervnih završetaka u koži) nakon terapije L tiroksinom iščezavaju, a kod nekih se održavaju (3), (5), (6), (7), (8) (9), (10), (11). Kod nekih pacijenata prve polineuropatske smetnje javljaju se tek više godina nakon započinjanja supstitucione terapije L tiroksinom (3). I to nezavisno od toga da li je uzrok hipotireoze autoimuna tireoidna bolest ili ne (3). Povezanost senzitivne polineuropatije i supkliničke hipotireoze ukazuje na činjenicu da i veoma suptilan deficit tireoidnih hormona može da izazove oštećenja perifernih nerava (4), (7), (8). Patogenetski mehanizam oštećenja perifernih nerava u hipotireozi nije u potpunosti rasvetljen. Smanjena raspoloživost visokoenergetskih fosfata za oksidativni metabolizam u mitohondrijama, uz smanjenu aktivnost Na+/K+ pumpe i promena od nje zavisnog aksonalnog transporta, verovatni su mehanizmi aksonalnog oštećenja u hipotireozi (11). Smanjen protok krvi u vasa nervorum zbog edema i povećane periferne vaskularne rezistencije moguć je doprinoseći faktor.

Činjenica da su se prvi simptomi polineuropatije kod naše pacijentkinje javili tek nakon početka supstitucione terapije levotiroksinom ukazuje na moguću analogiju sa reperfuzionim oštećenjima miokarda nakon uspešne reperfuzione terapije u akutnom infarktu miokarda i pojavom polineuropatije kod dijabetičara nakon nagle regulacije dijabetesa visokim dozama insulina.

Prvi simptom hipotireoze kod naše pacijentkinje bila je egzacerbacija hroničnog sinuzitisa usled edema ostijuma paranazalnih sinusa izazvanog nastupajućom hipotireozom. Zbog brzog produbljivanja hipotireoze terapija sinuzitisa nije davala efekat,a pacijentkinja je progresivne simptome u vidu zamora, malaksalosti i bezvoljnosti pripisivala upornom sinuzitisu. To je činjenica koja opominje da je hipotireoza izuzetno podmukla bolest, čak i onda kad nastaje naglo i kad se očekuje. I nikad se ne može predvideti šta će biti prvi simptom kod određenog bolesnika.

Tokom monoterapije L tiroksinom održavao se nefiziološki odnos između serumske koncentracije FT4 i FT3 (Tabela 4). Kod eutiroidnih ljudi sa zdravom štitnom žlezdom prosečan FT3/FT4 odnos je 0,32 (12). Kod naše pacijentkinje tokom monoterapije L tiroksinom 125 mcg/d ovaj odnos je bio 0,18 (Tabela 4). Nakon uvođenja kombinovane T4/T3 terapije ovaj odnos je 0,33 dva sata nakon uzimanja leka, što odgovara fiziološkom odnosu (Tabela 5). Tokom terapije L tiroksinom 125 mcg/d, serumska koncentracija FT4 je nešto iznad gornje referentne vrednosti, dok je serumska koncentracija TSH u granici normale, 2 h nakon uzimanja leka, što ukazuje na smanjenu osetljivost tireoidno-hipofizne negativne povratne sprege, kao posledice nemogućnosti periferne dejodinacije da nadomesti nedostajuću tireoidnu T3 sekreciju. (12) (Tabela 4). Vrednosti ukupnog i LDL holesterola tokom monoterapije L tiroksinom su povišene. (Tabela 4) Tokom kombinovane LT4/LT3 terapije dolazi do značajnog pada serumskih koncentracija ukupnog i LDL holesterola (Tabela 5). Monoterapija L tiroksinom, bez obzira na primenjenu dozu, nije bila u stanju da serumske koncentracije ukupnog i LDL holesterola vrati na nivo koji je postojao pre nastanka hipotireoze dok je pacijentkinja bila u eutireoidnom stanju na tireosupresivnoj terapiji ili pre toga u remisiji. Kombinovana LT4/ LT3 terapija omogućila je održavanje tih koncentracija upravo na tom nivou. To je indirektni dokaz da monoterapija L tiroksinom, bez obzira na primenjenu dozu, nije bila dovoljna da obezbedi onoliko aktivnog oblika tireoidnog hormona, trijodtironina koliko je neophodno da bi metabolizam holesterola bio onakav kakav je bio pre nastanka hipotireoze, kada je izvor tireoidnih hormona bila funkcionalna štitna žlezda. Nakon započinjanja kombinovane LT4/LT3 terapije pacijentkinja primećuje da ponovo ima tople šake. To bi mogla biti posledica jačeg dejstva kombinovane T4/T3 terapije na normalizaciju periferne vaskularne rezistencije, jer je serumska koncentracija FT3 jedini parametar tireoidne funkcije koji je nezavisno povezan sa vrednošću periferne vaskularne rezistencije kod hipertireoidnih pacijenata na tireosupresivnoj terapiji i hipotireoidnih pacijenata na supstitucionoj terapiji L tiroksinom (13). Serumske koncentracije TSH su bile približno iste tokom LT4 i kombinovane LT4/LT3 terapije (Tabela 4 i 5).

Tireoidni hormoni imaju veliku ulogu za održavanje normalne funkcije i integriteta centralnog i perifernog nervnog sistema. Imaju značajnu ulogu u regulaciji centralne noradrenergičke neurotransmisije, kao i u funkciji serotoninergičkog i dopaminergičkog sistema. Tireoidni hormoni se nalaze u visokoj koncentraciji u kortakalnom tkivu, a nasuprot perifernim tkivima gde koncentracije T4 daleko nadmašuju koncentracije T3, u mozgu se T4 i T3 nalaze u ekvimolarnom odnosu. Iz toga proizlazi izuzetan značaj adekvatnih intraneuronalnih koncentracija biološki najpotentnijeg hormona tireoidne žlezde, trijodtironina, za funkciju mozga (14).

Brojne eksperimentalne studije su pokazale ogroman značaj koji T3 ima za regeneraciju povređenih perifernih nerava, tako da se razmatra mogućnost njegove primene u terapiji povreda perifernih nerava (15), (16), (17), (18). Trijodtironin ima veći efekat na regeneraciju perifernih nerava nego bilo koji faktor rasta ili adhezioni molekul. On je najmoćnija neurotrofna supstanca u prirodi. To je posledica njegovog višestrukog dejstva na gensku ekspresiju većeg broja faktora rasta, međućelijskog matriksa i ćelijskih adhezionih molekula (19).

Najverovatniji uzrok polineuropatije kod naše pacijentkinje je nastanak akutnog jatrogenog miksedema usled nepravovremenog uvođenja supstitucijske terapije tireoidnim hormonima, što je posledica velike doze i prevelikog razmaka između preporučenih kontrola nakon primene terapijske doze radioaktivnog joda.

Među tireoidnim pacijentima na monoterapiji L tiroksinom postoje velike interindividualne razlike u kapacitetu konverzije T4 u T3 u serumu i u proseku imaju daleko niže serumske koncentracije FT3 u odnosu na osobe sa zdravom štitnom žlezdom (12). Populacione studije su pokazale da je serumska koncentracija FT3 parametar koji ima najveću interindividualnu varijabilnost od svih laboratorijskih parametara tireoidne funkcije (20). Trijodtironin ima osoben cirkadijalni ritam koji sa izvesnom vremenskom zadrškom prati cirkadijalni ritam TSH, što ukazuje na njegovo tireoidno poreklo i veliki fiziološki značaj (21). Kod naše pacijentkinje tokom monoterapije L tiroksinom istovremeno su se održavali simptomi polineuropatije i hipotireoidni simptomi od strane CNS-a. Tokom kombinovane T4/T3 terapije, hipotireoidni simptomi od strane CNS-a su gotovo u potpunosti nestali, a polineuropatske tegobe su se značajno smanjile. Moguće je da monoterapija L tiroksinom kod naše pacijentkinje nije bila u stanju da obezbedi dovoljnu serumsku koncentraciju FT3, koja bi obezbedila optimalnu intraneuronalnu koncentraciju T3 neophodnu za održanje normalne funkcije i strukturnog integriteta centralnog i perifernog nervnog sistema u skladu sa specifičnim tireoidnim fenotipom. Genetski polimorfizam na nivou D2 dejodinaza i tireoidnih transportera takođe bi mogao da modifikuje raspoloživost trijodtironina u nervnim ćelijama (22).

Potrebno je ostaviti mogućnost i za eventualnu ulogu autoimunosti u patogenezi polineuropatije. Kod pacijentkinje su pozitivna p-ANCA autoantitela u niskom titru verovatno postojala i ranije zbog dugotrajne terapije Propiltiouracilom (23). Anti TPO antitela su umereno, a zatim lako povišena nakon terapije radioaktivnim jodom.

Moguće je da su ona posledica autoimunizacije tokom raspada tireocita nakon terapije radioaktivnim jodom.

Rezultati studija indirektno ukazuju na metaboličku prirodu hipotireoidne neuropatije, a za sada nema dokaza u prilog teorijskoj mogućnosti autoimunog uzroka hipotireoidne neuropatije (3). Osim toga, prvi simptomi polineuropatije kod naše pacijentkinje javili su se u stanju preteške, naglo nastale, klinički manifestne hipotireoze, istovremeno sa mnogim drugim hipotireoidnim simptomima.

Zaključak

Slučaj koji smo prikazali ukazuje da terapija hipertireoze radioaktivnim jodom može dovesti do oštećenja perifernih senzitivnih nerava. Najverovatniji uzrok takvog oštećenja je razvoj akutnog miksedema zbog nepravovremenog uvođenja supstitucione terapije tireoidnim hormonima, a perzistiranje tih oštećenja tokom supstitucione terapije levotiroksinom mogao bi biti znak nedovoljnosti takve terapije ili pak ireverzibilnosti oštećenja perifernih nerava zbog težine hipotireoidnog stanja i velike brzine njegovog nastanka. Ostavljena je mogućnost i za ulogu tireoidne autoimunosti u patogenezi polineuropatije i malo verovatnog direktnog toksičnog dejstva radioaktivnog joda. Nakon primene terapijske doze radioaktivnog joda potrebne su daleko češće kontrole tireoidnih hormona nego što se preporučuju u kliničkoj praksi (2) (24), a lekari moraju biti svesni rizika koje neprepoznati nagli prestanak funkcije štitne žlezde i posledični brutalni metabolički sunovrat nose (25)(26).

Kombinovana T4/T3 terapija je kod naše pacijentkinje imala povoljne efekte na simptome hipotireoze vezane za centralni nervni sistem, dovela je do značajnog smanjenja serumske koncentracije ukupnog i LDL holesterola i do normalizacije odnosa serumskih koncentracija FT3 i FT4, makar u prvim časovima nakon primene leka. Takođe su se ispoljili i klinički znakovi sniženja, odnosno normalizacije periferne vaskularne rezistencije (tople šake). Dalje kliničko i ENG praćenje će pokazati kakav će biti dugoročni efekat ove terapije na hipotireoidnu senzitivnu polineuropatiju. Nikakvi neželjeni efekti nisu zapaženi tokom prvih šest meseci kombinovane T4, T3 terapije. Slučaj naše pacijentkinje višestruko ilustruje kompleksnost funkcionalnih poremećaja štitaste žlezde i izuzetnu složenost terapijskog pristupa, koji se, nažalost, u kliničkoj praksi često pojednostavljuje. (2) Klinički i laboratorijski parametri tokom monoterapije hipotireoze L tiroksinom i promena tih parametara tokom kombinovane LT4/LT3 terapije jasno ukazuju na prisustvo stalnog deficita trijodtironina tokom LT4 monoterapije kod naše pacijentkinje. S obzirom na ogroman značaj koji optimalna intraćelijska koncentracija trijodtironina ima za mnogobrojna tkiva i organe, a prvenstveno za nervni i kardiovaskularni sistem, hronični deficit trijodtironina bi se mogao veoma nepovoljno odraziti ne samo na kvalitet života nego i na morbiditet, prvenstveno kardiovaskularni i cerebrovaskularni, pa samim tim i na mortalitet (14),

(27). Povećan kardiovaskularni i cerebrovaskularni mortalitet, koji je pronađen u nekim studijama kod pacijenata koji su lečeni radioaktivnim jodom zbog hipertireoze, upravo bi mogao biti uzrokovan manjkavostima supstitucione terapije hipotireoze kod ovih pacijenata, a ne prethodnom davnašnjom hipertireozom kao što neki misle (2), (28), (29), (30).

Poseban etički problem koji stoji pred endokrinološkom zajednicom predstavlja činjenica da značajan broj pacijenata (10–15%), koji imaju hipotireozu nakon terapije hipertireoze radioaktivnim jodom ili operacijom ima doživotne hipotireoidne simptome uprkos supstitucionoj terapiji levotiroksinom, a o takvoj mogućnosti nisu bili pravovremeno obavešteni (30).

S obzirom na savremena saznanja o velikim interindividualnim genetskim razlikama na svim nivoima kompleksnog i nedovoljno proučenog tireoidnog sistema, potrebno je u lečenju funkcionalnih oboljenja štitaste žlezde imati individualni pristup pacijentu (20), (22), (31).

Slika 1. EKG na početku supstitucione terapije L tiroksinom

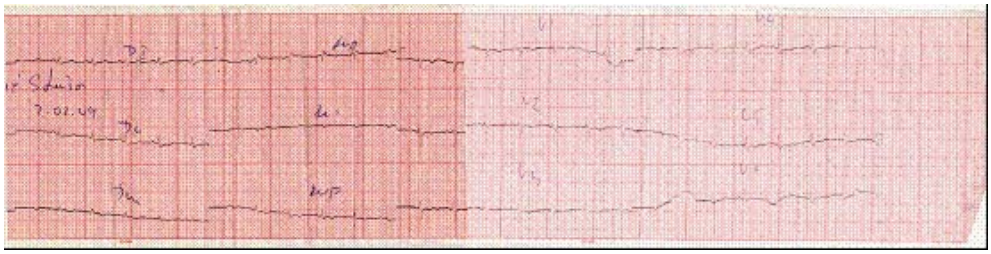

Tabela 1. Laboratorijske analize tokom hipotireoze

Analize	Vrednosti	Referentne vrednosti
FT4, pmol/l	2,6	9,1 – 23,9
TSH, mlU/l	75	0,27 – 4,2
CK, U/l	409	< 150
LDH, U/l	529	220 – 460
Holesterol, mmol/l	8,36	<5,2
LDL, mmol/l	5,9	<3,4
HDL, mmol/l	1,46	> 1,6
Trigliceridi, mmol/l	2,15	<1,7

Tabela 2. Laboratorijske analize tokom ispitivanja polineuropatije

Analize	Merenje 1	Merenje 2	Ref. vrednosti
Elektroforeza p.s.	Uredna		
Elektroforeza p.u.	Uredna		
Imunofiksacija p.s.	Uredna		
Imunofiksacija p.u.	Uredna		
HBsAg, anti HCV	Negativna		
ANA	Negativna		
p-ANCA	1:80	1:20	
Anti-MPO	9,2	7,7	<5U/ml
ANA SSA 52/60	56,6	5,0	<25U/ml
Antiparijentalna At	Negativna		
Endomizijalna At	Negativna		
Antiglijadinska At	Negativna		
Krioglobulini	Negativni		

Tabela 3. Elektroneurografski nalaz

	Terminalna latenca (ms)	Motorna brzina (ms)	Amplituda motornih EP (mV)	Senzitivna brzina (m/s)	Amplituda senzitivnih EP amp. (uV)	F talas latenca (ms)
n. medianus	2.8 (2.78+-0.41)	56.4 (58.78+-4.41)	10.2 (14.62+-8.45)	61.9 (60.88+-5.07) 63.8 (60.93+-5.17)	14 (30.93+- 12.07) 26 (22.74+-14.43)	24.8 (<30.142)
n. ulnaris						-
n. peroneus desno	4.2 (3.72+-0.53)	53.8 (49.51+-3.93) 53.7	1.0 (10.09+-4.81) 3.0			50,6 (< 52.292)
n. peroneus levo	4.8			45.5 (54.48+-5.16) 67.7 (49.3+-3.8)	2.9 (18.02+-8.27) 2.6 (10-30)	
n. suralis				51.9 (65.7+-3.7) 52.6 (56.7+-5.0)	2.3 (20.5+-6.1)	
n. cutaneus antebrachii medialis					11 (34.3+-14.2)	
n. peroneus superficialis						
n. radialis						

Tabela 4. Serumske koncentracije tireoidnih hormona i lipida tokom LT4 terapije

	Izmerene vrednosti		Ref. vrednosti	
	1. merenje	2. merenje		
FT4	22.8	16.14	12-22	pmol/l
FT3	4.21	4.15	3.1-6.8	pmol/l
TSH	0.57	1.70	0.27-4.2	mlU/L
FT3/FT4	0.18	0.26		
Holesterol	6.3	5.9	0-5.2	mmol/l
LDL	4.2	4.05	0-3.4	mmol/l
HDL	1.68	1.47	>=1	mmol/l
Trigliceridi	0.92	0.82	0-1.7	mmol/l

Uzorci seruma uzeti 2h nakon peroralne doze od 125 mcg L tiroksina (prvo merenje) i 100 mcg L tiroksina (drugo merenje)

Tabela 5. Serumske koncentracije tireoidnih hormona i lipida tokom kombinovane LT4/LT3 terapije (L tiroksin 100 mcg, L trijodtironin 10 mcg) podeljeno u 2 dnevne doze

	Izmerene vrednosti		Ref. vrednosti	
	1. merenje	2. merenje		
FT4	15.6	15.8	12-22	pmol/l
FT3	5.17	5.68	3.1-6.8	pmol/l
TSH	0.7	1.12	0.27-4.2	mlU/L
FT3/FT4	0.33	0.36		
Holesterol	5.38	5.44	0-5.2	mmol/l
LDL	3.6	3.5	0-3.4	mmol/l
HDL	1.41	1.48	>=1	mmol/l
Trigliceridi	0.76	0.96	0-1.7	mmol/l

Uzorci seruma uzeti 2 h nakon peroralne doze od 50 mcg LT4 I 5 mcg LT3 (prvo merenje) i nakon 3h drugom prilikom (drugo merenje)

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Staša Ivković*

THE ACUTE MYXEDEMA AFTER HYPERTHYROIDISM TREATED BY RADIOACTIVE IODINE AND ITS SEQUELAE

This is a case report of a female patient who developed, after radioactive iodine therapy for Grave's hyperthyroidism, a severe clinically manifested hypothyroidism, which was accompanied by predominantly sensory neuropathy of dominant axonal type. Besides symptoms and neurophysiological signs of polyneuropathy, the patient, in spite of seemingly adequate levothyroxine monotherapy for hypothyroidism during the last 2 years, still manifested persistent hypothyroid symptoms by CNS, higher serum concentrations of total and LDL cholesterol and clinical signs of the increased peripheral vascular resistance. Non-physiological serum FT3 and FT4 ratio was maintained, together with serum TSH and FT4 concentrations, which suggested lower sensitivity of thyroid-hypophyseal negative feedback.

The introduced combined LT4/LT3 substitution therapy resulted in quick subsidence of CNS-related hypothyroid symptoms, significant reduction of serum concentrations of total and LDL cholesterol, FT3/FT4 ratio normalization, at least in the first hours of drug administration, and disappearance of clinical signs of the increased peripheral vascular resistance. The extent of polyneuropathic difficulties was reduced to the level of not disturbing the sleep. Time and control ENG will show the final effects of combined T4/FT3 therapy on the peripheral nerve injuries. In the first 6 months, no adverse effects of this therapy were recorded.

Key words: radioactive iodine, hypertyroidism, polyneuropathy, hypothyroidism, T4/T3 therapy

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Introduction

Radioactive iodine therapy is considered very reliable and safe treatment in case of definitive management of autoimmune hyperthyroidism – Grave's disease. It is often used in the USA as the initial therapy of this disease. Expert literature reports that the only possible complication is a development of permanent hypothyroidism; therefore, many authors believe that an early onset of hypothyroidism is desired objective of therapy, given that, from long-term aspect, it is impossible to avoid such outcome; yet, hypothyroidism is allegedly very easy to treat (1).

Case Report

This is a case report of 41-old female patient treated by radioactive iodine for Grave's disease. The patient was diagnosed with hyperthyroidism in her 28 years of age. She was medicamentously treated with propylthiouracil for a long time. Remission ensued after 6 years of treatment. Three years later, the disease recurred. In the following 3 years, the same therapy was repeated, followed by radioactive iodine in a dose of 11mCi. Three months later, the patient was in euthyroid state. She was extremely well and symptom-free. The next control was scheduled in 3 months. Nevertheless, some ten days later, the patient manifested exacerbation of the chronic sinusitis and was treated several weeks without any success. This period was featured by fatigue, asthenia, indisposition and hoarseness. Seven weeks after the previous control visit, she had sudden deterioration of her general health condition, reflecting in fatigue and tachycardia. Laboratory test results indicated severe hypothyroidism: TSH - 60 ml U/l, and FT4 2.6 pmol/l (Table1). Soon after the onset of levothyroxine substitution therapy, neurological symptoms were developed. Sudden symmetrical hand paresthesia made patient waking from her sleep. At the same time, continuous sensation of straining and burning of the anterior abdominal wall was present. In addition, severe symptoms of hypothyroidism of all organ systems were manifested in the following two months as well as often attacks of feeling of suffocation and tachycardia, sleep apnea syndrome, panic attacks for several times, hoarseness, asthenia, depression, vertigo, discrete dysarthria, and difficulty with swallowing. ECG showed remarkably low-voltage, diffuse flattening and biphasic T waves with slightly widened QRS complex (Figure 1). Echocardiographic finding was normal. Laboratory analyses showed higher CK and serum cholesterol values.

After reaching the laboratory euthyroid state, paresthesias became generalized and permanent, and gradually gained the quality of neuropathic pains. Neurological findings were regular. The initial ENG failed to verify the signs of polyneuropathy. Serum and urine protein electrophoresis was normal. Serum and urine protein immunofixation was also normal. HBs Ag and anti HCV antibodies were negative.

Immunological analyses showed the presence of p-ANCA antibodies in titre with the initial finding of 1:80, and then 1:20, and finally negative, and anti MPO antibodies were slightly increased -7,7 U/ml (upper limit to 5U/ml). ANA antibodies were negative, and only once anti Ro SSA antibodies were found mildly higher - 56 U/ml(normal to 25U/ml), but several months later, the results were normal – 5 U/ml. Antiparietal, antigliadin and endomysial antibodies were negative. Cryoglobulins were negative. Serum immunoglobulins were normal. Immune complexes were not present. Glucose stress test was normal (Table 2).

Upon neurological evaluation, thyroid small fiber polyneuropathy was presumed and symptomatic Lyrica and Amitriptyline oral therapy was recommended, but due to adverse effects and inadequate efficacy, the therapy was discontinued after 4 weeks.

Two years after radioactive iodine therapy, the ENG findings suggested to more sensory, dominant axonal neuropathy of smaller fibers in the upper and lower extremities (Table 3).

In spite of substitutional levothyroxine 125 mcg/day therapy and serum TSH concentration of about 1 mlU/l, her asthenia, lower concentration, obliviousness, depression and generalized neuropathic pains persisted. Ratio of serum FT3/FT4 concentrations was decreased. In addition, higher serum total and LDL cholesterol levels were also persistent.

An expert opinion of thyreodologist was that polyneuropathy could not be associated with either hypothyreosis or therapeutical procedures, and that polyneuropathy should be treated exclusively by neurologist; and, her depressive symptoms ought to be managed by psychiatrist.

Two-and-a half years after the onset of hypothyroidism, combined L thyroxin 100mcg and L triiodothyronine 10mcg therapy was introduced, divided in 2 daily doses. Very soon, CNS-related hypothyroid symptoms subsided. The extent of polyneuropathic difficulties, during the first six months of combined therapy, was very gradually decreased to the level not disturbing the sleep. Moreover, the patient noted that her hands were again warm, in distinction from former two winters when she was covered by L thyroxin monotherapy. Serum FT3/FT4 ratio was also restored to normal, at least within the first hours of drug administration (Table 5). Serum TSH levels were almost the same in monotherapy L thyroxin 125mcg/day and combined T4/T3 therapy (Tables 4 & 5).

Discussion

The association between polyneuropathy and hypothyroidism is not widely known among endocrinologists. There is even the internet site where these patients exchange their experience, complaining of the same problem that their endocrinologists fail to

see the connection between hypothyroidism and polyneuropathy (1). Nevertheless, one may find an extensive literature addressing this issue. Sensory polyneuropathy appear in both untreated and treated clinical, even subclinical hypothyroidism, regardless of the cause of hypothyroidism. (3),(4),(6),(7),(8),(9),(10),(11)

Ettore Beghi and assoc. found that 64% of 39 patients with primary hypothyroidism of different causes, duration and not depending upon the beginning of treatment, had subjective polyneuropathic difficulties, and electroneurographic diagnosis of polyneuropathy was established in 72% of cases (3).

Flavia Magri and assoc. found lowered density of intraepidermal nerve fibers in 60% of patients with the untreated clinical hypothyroidism and in 25% with the untreated subclinical hypothyroidism (4), and they documented the increase of intraepidermal nerve fibers density in these patients after L thyroxin therapy (5).

Kristin Orstavik and assoc. concluded that some patients with treated hypothyroidism had the symptoms of small fibre neuropathy (6).

Penza P and assoc. described the case of a female patient whose symptoms of small fibre polyneuropathy were the first signs of subclinical hypothyroidism. Substitution levothyroxine therapy resulted in complete clinical and neuropathological recovery (7).

Fabio Monzani and assoc. established high frequency of neuromuscular symptoms in patients with subclinical hypothyroidism and recovery following the introduction of substitution levothyroxine therapy (8).

D.J.Dick and assoc. described a patient with the sensory neuropathy as the only symptom of severe hypothyroidism. Substitution L thyroxin therapy led to complete clinical and ENG recovery (9).

Accordingly, sensory neuropathy may be caused by hypothyroidism. It is given little thought to because it is very often mild, and patients even miss to mention the symptoms, and it is also often subclinical (4). In some patients, subjective symptoms and objective signs (pathological ENG finding and reduced density of peripheral nerve endings on the skin) subside after L thyroxin therapy, and in some they tend to be persistent (3),(5) (6),(7),(8),(9), (10),(11). Some patients have the first polyneuropathic disorders only few years after the beginning of substitution levothyroxine therapy (3), independently from whether the cause of hypothyreosis is an autoimmune thyroid disease or not (3). The association of sensory polyneuropathy and subclinical hypothyroidism points to the fact that even very subtle deficit of thyroid hormones may cause damage of peripheral nerves (4),(7),(8). Pathogenetic mechanism of peripheral nerve damage in hypothyroidism has not been fully clarified. Diminished mitochondrial availability of high-energy phosphates for oxidative metabolism, along with lower activity of Na+/K+ pump and change of activity-dependent axonal transport are probable causes of axonal damage in hypothyroidism (11). Reduced blood flow in vasa nervorum due to edema and increased peripheral vascular resistance is a probable contributing factor.

The fact that the first symptoms of polyneuropathy appeared in our patient not before the onset of substitution levothyroxine therapy suggested to possible analogy with the reperfusion lesions to the myocardium after successful reperfusion therapy in the acute myocardial infarction, and with the development of polyneuropathy in diabetics after the abrupt diabetes regulation by high insulin doses.

In our patient, the initial symptom of hypothyroidism was exacerbation of chronic sinusitis due to edema of paranasal sinus ostium caused by imminent hypothyroidism. Because of rapid worsening of hypothyroidism, therapy for sinusitis was ineffective, and the patient ascribed her fatigue, asthenia and apathy to persistent sinusitis. This is the fact which gives a warning that hypothyroidism is an extremely insidious disease, even if it appears abruptly and is actually expected. In addition, you can never predict the first symptom in the respective patient.

During the L thyroxin monotherapy, non-physiological serum FT3 and FT4 ratio was maintained (Table 4). In euthyroid people with healthy thyroid gland, mean FT3/FT4 ratio is 0.32(12). In our patient during monotherapy with L thyroxin 125 mcg/day, this ratio was 0.18 (Table 4). Upon introduction of T4/T3 therapy, this ratio was 0.33 two hours after the drug administration, corresponding to physiological ratio (Table 5). During L thyroxin 125 mcg/day therapy, serum FT4 was slightly above the upper reference limit, while serum TSH concentration was within the limits 2 hours after drug ingestion, indicating reduced sensitivity of thyroid-hypophyseal negative feedback as a consequence of inability of peripheral deiodination to compensate for lack of thyroid T3 secretion (12) (Table 4). Total and LDL cholesterol values during L thyroxin monotherapy were increased. (Table 4). During combined LT4/LT3 therapy, a significant fall of serum total and LDL cholesterol concentrations were present (Table 5). L thyroxin monotherapy, regardless of the applied dose, failed to restore serum total and LDL cholesterol values to the level before hypothyroidism or time when the patient was in euthyroid state on thyroid suppressive therapy or before that in remission. Combined LT4/LT3 therapy enabled to maintain these concentrations just on that level. It was an indirect confirmation that L thyroxin monotherapy, regardless of the applied dose, was not sufficient to provide as much active thyroid hormone, triiodothyronine, as required for cholesterol metabolism to be as it was before the onset of hypothyroidism , when thyroid hormones originated from functional thyroid gland. After the beginning of combined LT4/LT3 therapy, the patient noticed that her hands were again warm. It could be the consequence of stronger effect of combined T4/T3 therapy to normalization of peripheral vascular resistance, because serum FT3 concentration is the only thyroid function parameter which is indirectly associated with the peripheral vascular resistance value in hyperthyroid patients covered by thyroid suppression therapy and in hypothyroid patients on substitution L thyroxine therapy (13). Serum TSH concentrations were approximately the same during LT4 and combined LT4/LT3 therapy (Tables 4 and 5).

Thyroid hormones have major role in maintaining the normal function and integrity of the central and peripheral nervous system. It has a significant role in the regulation of the central noradrenergic neurotransmission as well as function of serotonergic and dopaminergic systems. Thyroid hormones may be found in high concentrations in the cortical tissue, opposite to peripheral tissues where T4 concentrations far exceed T3 concentration, namely T4 and T3 are in equimolar ratio in the brain. It accordingly follows that adequate intraneuronal concentrations of biologically most potent thyroid hormone, triiodothyronine, have an extreme significance for brain functioning (14).

Numerous experimental studies have shown the significance of T3 in regeneration of injured peripheral nerves, and therefore, its application in the respective therapy has been considered (15),(16),(17),(18). Triiodothyronine has larger effect on regeneration of peripheral nerves than any growth factor or adhesion molecule. It is the most potent neurotrophic substance in nature. It is the result of its multiple effects on gene expression of a number of growth factors, intercellular matrix and cell adhesion molecules (19).

The most probable cause of polyneuropathy in our patient was the acute iatrogenic myxedema due to ill-timed introduction of substitution therapy with thyroid hormones, what was the consequence of high dose and too large interim period between recommended controls after the application of therapeutical radioactive iodine doses. There are major interindividual differences in the capacity of serum T4 and T3 conversion among athyroid patients on L thyroxin monotherapy, and on the average, they have far lower serum FT3 concentrations in relation to individuals with healthy thyroid gland (12). Population studies have shown that serum FT3 concentration is a parameter with the highest interindividual variability of all laboratory parameters of thyroid function (20). Triiodothyronine has a distinctive circadian rhythm, which follows TSH circadian rhythm with certain time delay, suggesting its thyroidal origin and great physiological significance (21). During L thyroxin monotherapy in our patient, the symptoms of polyneuropathy and hypothyroid symptoms related to CNS maintained simultaneously. During combined T4/T3 therapy, the aforementioned symptoms almost completely disappeared, and polyneuropathic problems were significantly reduced. It is possible that L thyroxin monotherapy in our patient could not ensure enough serum FT3 concentration to reach optimal intraneuronal T3 concentration necessary for maintaining the normal function and structural integrity of the central and peripheral nervous system according to specific thyroid phenotype. Genetic polymorphism at the level of D2 deiodinase and thyroid transporters could also modify triiodothyronine availability in nerve cells (22).

One should also consider the probable role of autoimmunity in pathogenesis of polyneuropathy. It is possible that our patient had low titre positive p-ANCA antibodies even earlier because of long-term therapy with Propylthiouracil (23). Anti TPO

antibodies were moderately and then slightly increased after radioactive iodine therapy. Probably, these were the sequelae of autoimmunization during the disintegration of thyreocytes after radioactive iodine therapy.

Study results indirectly suggest to metabolic nature of hyperthyroid neuropathy, and so far, there has not been any scientific evidence for the autoimmune-related nature of hypothyroid neuropathy (3). Moreover, the initial symptoms of polyneuropathy appeared in our patient when she was in the condition of most severe, sudden and clinically manifested hypothyroidism, concurrently with many other hypothyroid symptoms.

Conclusion

The presented case report suggests that radioactive iodine therapy for hyperthyroidism may cause damage of peripheral nerves. The most probable cause of such injury is a development of the acute myxedema due to ill-timed introduction of substitution therapy with thyroid hormones; persistence of these lesions during substitution levothyroxine therapy could be a sign of inadequacy of such therapy or irreversibility of damage of the peripheral nerves because of severity of hypothyroid condition and its rapid occurrence. One should also consider a possibility of the role of thyroid autoimmunity in pathogenesis of polyneuropathy and low probability of direct toxic effect of radioactive iodine. After the application of therapeutical radioactive iodine doses, the controls for thyroid hormone levels are far more frequently required than recommended in clinical practice (2), (24), and the doctors must be aware of the risk of unrecognized dysfunction of thyroid gland and consequential brutal metabolic collapse (25)(26).

In our patient, combined T4/T3 therapy had favorable effects on hypothyroid symptoms related to the central nervous system; it led to significant reduction of serum total and LDL cholesterol levels and normalization of serum FT3 and FT4 concentration ratio, at least in the first hours after drug administration. In addition, the clinical signs of decrease, that is, normalization of peripheral vascular resistance (warm hands) were manifested, too. Further clinical and ENG monitoring will show the long-term effect of this therapy on hypothyroid sensory polyneuropathy. No side effects were recorded in the first six months of combined T4/T3 therapy.

The case of our patient illustrates in multiple ways the complexity of functional impairments of thyroid gland, and an extraordinary complexity of therapeutical approach, which has been, unfortunately, simplified too often in clinical practice (2). Clinical and laboratory parameters during L thyroxin monotherapy for hypothyroidism and the change of these parameters during combined LT4/LT3 therapy clearly point to presence of continuous deficit of triiodothyronine during LT4 monotherapy in our patient. Considering a huge significance of an optimal intracellular triiodothyronine

concentration for many tissues and organs, and primarily for nervous and cardiovascular systems, the chronic triiodothyronine deficiency may unfavorably reflect on both the quality of life and morbidity, before all cardiovascular and cerebrovascular one, and consequently to mortality rate as well (14)(27). Higher cardiovascular and cerebrovascular mortality rates reported by some studies in patients treated by radioactive iodine for hyperthyroidism could be caused by disadvantages of substitution levothyroxine therapy in these patients rather than by some ancient hyperthyroid state as believed by some authors (2),(28),(29)(30).

A special ethical issue facing the endocrinology community is the fact that a considerable number of patients (10-15%) with hypothyroidism, after their therapy with radioactive iodine or surgery, have long-life hypothyroid symptoms in spite of substitution levothyroxine therapy, and that they have not been informed on such problem on time. (30)

Given the contemporary knowledge on large interindividual genetic differences at all levels of complex and insufficiently studied thyroid system, it is necessary to exercise an individual approach to patient in the management of functional disorders of thyroid gland (20), (22), (31).

Figure 1. ECG on the beginning of substitutional L thyroxine therapy

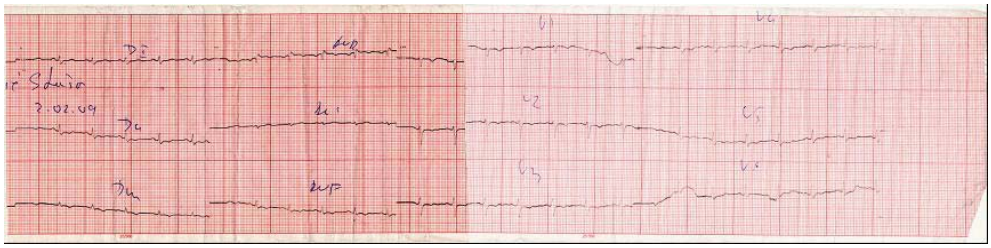

Table 1. Laboratory analyses during hypothyroidism

Analysis	Values	Reference values
FT4, pmol/l	2,6	9,1 – 23,9
TSH, mlU/l	75	0,27 – 4,2
CK, U/l	409	< 150
LDH, U/l	529	220 – 460
Cholesterol, mmol/l	8,36	<5,2
LDL, mmol/l	5,9	<3,4
HDL, mmol/l	1,46	> 1,6
Triglycerides, mmol/	12,15	<1,7

Table 2. Laboratory analyses during examination of polyneuropathy

Analysis	Measurement 1	Measurement 2	Reference values
Serum protein electrophoresis	Regular		
Urine protein electrophoresis	Regular		
Serum protein immunofixation	Regular		
Serum protein immunofixation	Regular		
HBsAg, anti HCV	Negative		
ANA	Negative		
p-ANCA	1:80	1:20	
Anti-MPO	9.2	7.7	<5U/ml
AntiRo SSA 52/60	56.6	5.0	<25U/ml
Antiparietal At	Negative		
Endomysial At	Negative		
Antigliadin At	Negative		
Cryoglobulins	Negative		

Table 3. Electroneurographic findings

	Terminal latency (ms)	Motor velocity (ms)	Motor EP amplitudes (mV)	Sensory conduction velocity (m/s)	Sensory EP amplitudes (uV)	F wave latency (ms)
n. medianus	2.8 (2.78+-0.41)	56.4 (58.78+-4.41)	10.2 (14.62+-8.45)	61.9 (60.88+-5.07) 63.8 (60.93+-5.17)	14 (30.93+- 12.07) 26 (22.74+-14.43)	24.8 (<30.142)
n. ulnaris						-
n. peroneus dexter	4.2 (3.72+-0.53)	53.8 (49.51+-3.93) 53.7	1.0 (10.09+-4.81) 3.0			50,6 (< 52.292)
n. peroneus sinister	4.8			45.5 (54.48+-5.16)	2.9 (18.02+-8.27)	
n. suralis				67.7 (49.3+-3.8) 51.9 (65.7+-3.7) 52.6 (56.7+-5.0)	2.6 (10-30) 2.3 (20.5+-6.1)	
n. cutaneus antebrachii medialis					11 (34.3+-14.2)	
n. peroneus superficialis						
n. radialis						

Tabela 4. Serumske koncentracije tireoidnih hormona i lipida tokom LT4 terapije

	Measured values		Reference values	
	1. measurement	2. measurement		
FT4	22.8	16.14	12-22	pmol/l
FT3	4.21	4.15	3.1-6.8	pmol/l
TSH	0.57	1.70	0.27-4.2	mlU/L
FT3/FT4	0.18	0.26		
Cholesterol	6.3	5.9	0-5.2	mmol/l
LDL	4.2	4.05	0-3.4	mmol/l
HDL	1.68	1.47	>=1	mmol/l
Triglycerides	0.92	0.82	0-1.7	mmol/l

Serum samples collected 2h after oral dose of L thyroxine 125 mcg (1. measurement) and L thyroxine 100 mcg (2. measurement)

Table 5. Serum concentrations of thyroid hormones and lipids during combined T4/T3 therapy (L thyroxin 100 mcg, triiodothyronine 10 mcg) divided in 2 daily doses

	Izmerene vrednosti		Ref. vrednosti	
	1. merenje	2. merenje		
FT4	15.6	15.8	12-22	pmol/l
FT3	5.17	5.68	3.1-6.8	pmol/l
TSH	0.7	1.12	0.27-4.2	mlU/L
FT3/FT4	0.33	0.36		
Cholesterol	5.38	5.44	0-5.2	mmol/l
LDL	3.6	3.5	0-3.4	mmol/l
HDL	1.41	1.48	>=1	mmol/l
Triglycerides	0.76	0.96	0-1.7	mmol/l

Serum samples collected 2 h after oral dose of LT4 50 mcg and LT3 5 mcg (1. measurement) and after 3h (2. measurement)

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