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SVIM SPOREDNIM PUTEVIMA DO IZLEČENJA HIPERTIREOZE – ZAMKE I MOGUĆNOSTI

Apstrakt: Prikazana je pacijentkinja AJ, 36 godina, kod koje je hipertireoza lečena na manje uobičajenim terapijskim modelima, a nakon razvoja neželjenih reakcija na tireosupresivnu medikamentoznu terapiju. Postoje tri osnovna modaliteta u lečenju tireotoksikoze: medikamentna terapija tireosupresivima, ablacija radioaktivnim jodom i hirurško lečenje – tiroidektomija. Pacijenti kod kojih se ne postigne adekvatna kontrola tirotoksikoze imaju visok mortalitet usled mogućnosti razvoja tiroidne oluje. Primena medikamentne terapije hipertireoze, kao prve linije lečenja, udružena je sa pojavom različitih neželjenih efekata. Neželjeni efekti Metimazola su doзно zavisni, dok u slučaju primene Propiltiouracila nastanak neželjenih efekata nije jasno zavisao od doze. U slučaju opisane pacijentkinje bili su primenjeni svi alternativni, manje poznati modaliteti lečenja hipertireoze, nakon pojave neželjenih reakcija na tireosupresivnu terapiju. Natrijum-perhlorat, tj. natrijumova so perhlorne kiseline se retko koristi u lečenju hipertireoidizma, kao u slučajevima teških idiosinkratičnih reakcija na tionamide, agranulocitoze, hepatitisa, ako nije postignuto eumetabolično stanje i nije moguća aplikacija terapijske doze radijoda. Primenuje se u vidu rastvora, najčešće 8%. U težim oblicima bolesti, kada je hipertireoidizam veoma izražen, daje se 4 do 6 puta po 10 do 15 kapi dnevno i doza se smanjuje nekada do minimalne doze održavanja. Terapijska razmena plazme (TPE) je vantelesna tehnika prečišćavanja krvi dizajnirana za uklanjanje supstanci velike molekularne težine vezanih za proteine plazme (patogena auto-antitela, imunokompleksi, krioglobulini, mijelomični laki lanci, endotoksini, holesterol koji sadrže lipoproteini i tiroidni hormoni). Efikasnost lečenja zavisi od volumena krvi koja se obrađuje, zapremine plazme koja se razmenjuje u svakom procesu, broja izvedenih procedura, učestalosti razmene i brzine mobilizacije, stabilizacije i ponovne sinteze ćelija ili komponenti plazme. TPE je efikasan alternativni tretman koji daje mogućnost pripreme pacijenata za definitivno lečenje: ablativnu terapiju poput RAI ablacije ili tireoi-

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dektomiju. Terapijska plazmafereza, ako se izvodi u specijalističkim centrima, sigurna je, brza i efikasna metoda.

Ključne reči: hipertireoza, neželjene reakcije, kalijum jodid, natrijum perhlorat, terapijska izmena plazme

Prikaz slučaja

Pacijentkinja AJ, 36 godina, žali se na gubitak TT, nervozu, nesanicu, znojenje, podrhtavanje ruku, izostanak menstruacije. Anamnestički, hipertireoza dijagnostikovana u junu 2019, kada je uveden Tiastat u terapiju, nakon čega su se javile promene na koži, karakteristika urtikarije, te je lek zamenjen za Propiltiouracil (PTU). Nedugo po uvođenju leka javlja se grebanje u grlu, kožne manifestacije tipa eritema, primetila je da su joj požutele beonjače, dijagnostikovao je medikamentozni hepatitis, nakon čega je terapija obustavljena, te ubrzo dolazi do normalizacije hepatograma. U ličnoj anamnezi navodi alergiju na polen, pušač je, porodična anamneza je bez osobenosti. Pacijentkinja je svesna, orijentisana u vremenu, prostoru i prema licima, TT 62 kg, TV 171 cm, BMI 21 kg/m², afebrilna, u miru eupnoična, acijanotična, uredno prebojene, baršunaste, preznojene kože, uredno hidrirana, bez periferne limfadenopatije, izraženih eflorescenci i znakova hemoragijskog sindroma. Vrat cilindričan, aktivno i pasivno pokretan. Vene vrata neupadljive, nad karotidama nema šuma. Štitasta žlezda uvećana, meka, palpatorno bolno neosetljiva, pokretna pri gutanju, bez palpabilnih nodusa i regionalnih limfnih nodusa. Perkutorno prisutna sonornost, auskultatorno normalan disajni šum, bez propratnog nalaza. Srčana radnja aritmična, fr 120 /min, tonovi tiši, TA 100/60 mmHg. EKG: Sinusna tahikardija, fr. 24 u min., bez promena u ST segmentu ili T talasu. Radiografija srca i pluća uredna. Ultrazvuk vrata: Štitasta žlezda je niže položena, uvećana, istmus debljine oko 10 mm. Parenhim žlezde je hipoehogen, homogen, pojačanog CD signala, pseudonodularan. Paratrahealno LN promera do 10 mm. U jugularnim lancima nema patološki izmenjenih limfnih nodusa. Obe submandibularne i parotidne žlezde homogene ehostrukture, bez fokalnih promena (TIRADS DL1 LL1). Ultrazvuk abdomena urednog nalaza. Tiroidni status na prijemu: Tireostimulirajući hormon (TSH): <0.005 mIU/L [0.27–4.2], Tiroksin slobodan (fT4): >100.0 pmol/L [12.0–22.0], Trijodtironin slobodan (fT3): 44.85 pmol/L [3.1–6.8], Antitela na tireoidnu peroksidazu (anti-TPO): 66.0 IU/L [0.0–34.0], Antitela na tireoglobulin (anti-TG): 632.0 IU/L [0.0–115.0] TSH receptorska antitela: 7.0 IU/L.

U terapiju uveden KJ (Kalijum jodid, Lugolov rastvor), 3 x 7 gtt uz Pronison tbl 20+10 mg. Tiroidni status progresivno: fT4: 77.8... 60.9.... 44.5.... 41.3 pmol/L, fT3: 19.33... 13.55.... 10.45... 10.41 pmol/L. U daljem toku bolesti 18. dana nakon uvođenja terapije dolazi do izmicanja efektima KJ: FT4 44.4, FT3 22.1 pmol/l. Pacijentkinja na sopstveni zahtev i odgovornost biva otpuštena, da bi u kućnim uslovima sprovodila terapiju Na-perhloratom (NaClO₄) u dozi 4 x 15 gtt, a zatim 5 x

21 gtt, nakon čega dolazi do razvoja febrilnosti, dijareje i leukocitopenije, u sklopu neželjenih reakcija na lek. Terapija NaClO_4 je obustavljena i nastavljeno je lečenje visokim dozama beta blokatora do hospitalizacije. Odmah po obustavljanju terapije tegobe i febrilnost su se povukle. Urađen je test fiksacije radioaktivnog joda (RAI), procenat fiksacije nakon 24h: 56.4%. Doneta je odluka o lecenju radioaktivnim jodom, uz prethodnu primenu plazmafereze. Terapijska izmena plazme (TPE, Therapeutic Plasma Exchange) sprovedena je u pet ciklusa, bez neželjenih događaja, uz adekvatan odgovor i pad koncentracije tiroidnih hormona ($\text{FT3} > 50 \text{ pmol/l} \dots 5.92 \text{ mol/l}$, $\text{FT4} > 100 \text{ pmol/l} \dots 15.9 \text{ pmol/l}$). Pacijentkinja je upućena u Centar za nuklearnu medicinu, KCS, gde je primila terapiju radiojodom, nakon čega su u terapiju uvedene Pronison tbl 2 x 20 mg. Pacijentkinja je otpuštena u dobrom opštem stanju, biohemijski eutiroidna, uz terapiju: Propranolol tbl 3x60 mg, Pronison tbl 20+10 mg, Nolpaza tbl 40 mg, uz redovne kontrole na 14 dana.

Diskusija

Primena medikamentne terapije hipertireoze, kao prve linije lečenja, udružena je sa pojavom različitih neželjenih efekata. Neželjeni efekti Metimazola su doznno zavisni, dok u slučaju primene Propiltiouracila nastanak neželjenih efekata nije jasno zavisn od doze. Neželjeni efekti se mogu podeliti na „minor” i „major” oblike. „Minor” ili blagi neželjeni efekti se javljaju sa podjednakom zastupljenošću kod oba leka. Obuhvataju kožne promene (obično urtikariju ili makuloznu ospu) koje se javljaju u 4–6%, gastrointestinalne tegobe (1–5%), artralgijs (1–5%) i blage tranzitorne granulocitopenije sa podjednakom zastupljenošću za obe vrste leka. Veoma retko se mogu javiti i promene ukusa i mirisa, sialadenitis i glavobolje. Blage kožne reakcije se mogu rešiti dodavanjem antihistaminika, dok se terapija tireosupresivima nastavlja. Alternativno, pacijent se može prevesti sa jednog antitiroidnog leka na drugi. Međutim, ukrštena reakcija može postojati u oko 50%. Nastanak artralgijs, iako spada u „minor” neželjene efekte, zahteva hitno ukidanje leka, s obzirom na to da može dovesti do veoma teškog migratornog poliartritisa poznatog kao „antitiroidni artritis sindrom”. „Major” ili teški neželjeni efekti se javljaju u 0,2–0,5% lečenih pacijenata i podrazumevaju poliartritis, ANCA pozitivni vaskulitis, hepatotoksičnost (imunoalergijski hepatitis iolestaza), agranulocitoza i veoma retko trombocitopenija, aplastična anemija, hipoprotrombinemija, pankreatitis i hipoglikemija. Tokom 1993. g. je objavljena moguća udružnost antimijeloperoksidaza antineutrofilnih citoplazmatskih antitela (MPO-ANCA) sa primenom antitiroidnih lekova uz mogućnost da antitela na mikrozomne antigene, koji se sastoje uglavnom od tiroidne peroksidaze, mogu ukršteno reagovati sa MPO. Hepatotoksičnost je još jedna teška komplikacija antitiroidne terapije, koja se javlja u 0,1–0,2% slučajeva. Postoje dva tipa medikamentne hepatotoksičnosti i to su direktna toksičnost i idiosinkrazija. Antitiroidni lekovi

dovode do lezije jetre po tipu idiosinkrazije. Nastanak lezije je nepredvidiv, odgovor nije dozno zavisen i može nastati bilo kada tokom uzimanja terapije. Ekstrahepatične reakcije hipersenzitivnosti, kao što su osip, groznica, artralgiya, leukocitoza i eozinofilija postoje kod četvrtine pacijenata, što zajedno sa tokom bolesti sugerise da se radi o imunološki posredovanim reakcijama. Skorašnji rezultati pokazuju da u većini slučajeva i u idiosinkratskim reakcijama postoji direktna hepatotoksičnost, ali uzrokovana metabolitima češće nego intaktnim lekovima. Lek ili njegov metabolit se vezuju za ćelijsku komponentu domaćina stvarajući haptenu, a imuni odgovor na ovaj neoantigen ima ulogu u patogenezi lezije jetre. Metimazol i Karbimazol izazivajuolestazu, dok Propiltiouracil izaziva nekrozu hepatocita. S obzirom na različite mehanizme hepatotoksičnosti u daljem lečenju je moguća primena alternativnog anti-tiroidnog leka. Agranulocitoza je najozbiljnija komplikacija tireosupresivne terapije.

Primena stabilnog jodida u terapiji hipertireoze poznata je od ere Von Basedova (1840) i Trousseaua (1863) (1–5). Iako je jodid korišćen tokom 19. i početkom 20. veka, ovaj oblik terapije je široko prihvaćen nakon pronicljivih zapažanja Neisera (1920), Loevija i Zondeka (1921) i Plummera (1923) (1,4). Naime, Plummer je u terapiju uvodio 10 kapi Lugolovog rastvora koji sadrži 5% I_2 i 10% kalijum-jodida (KI), u dozi približno 80–320 mg joda dnevno (5). Počev od 1930-ih, Thompson i saradnici (2) izvestili su o zadovoljavajućim rezultatima nakon što su pacijentima davali približno 6 mg joda dnevno u 64% blagih i 10% teških slučajeva Graves-Basedove hipertireoze.

Međutim, medicinska literatura sadrži obilje referenci o rizicima davanja supstrata joda pacijentima sa hipertiroidizmom. Terapija jodidom je donosila privremeno olakšanje, ali izmicanje od njegovih efekata pogoršavalo je kliničko stanje pacijenta (1). Stanbury 1998. izveštava o jodom izazvanoj hipertireozu, ali kao o komplikaciji koja je nastala kada je jod davan za endemsku strumu (6), osim nekoliko izveštaja i u neendemskom području (7). Nakon uvođenja terapije tionamidima i radioaktivnim jodom (RI), jodid se nije koristio u medicinskom lečenju hipertireoze (1).

Nakon uvođenja esejaja za određivanje tiroidnih hormona i nivoa TSH, početni efekti viška jodida (150–456 mg) na snižavanje nivoa T4 u serumu potvrđeni su u većini studija (8–12). Iako su zabeleženi trajno povišeni nivoi T3 i pojava "escape" mehanizma nakon 2–14 nedelja (8, 9), neki pacijenti su postigli eutiroidno stanje i održavali normalne nivoe T4 i T3 tokom nekoliko meseci (8, 9).

Zanimljivo je da su mehanizmi inhibitornog dejstva viška jodida na štitastu žlezdu razjašnjeni nakon što je upotreba jodida postala manje uobičajena za medicinsko lečenje hipertireoze, osim za preoperativnu pripremu ili u tirotoksičnoj krizi. 1948. godine Volff i Chaikoff (21) izvestili su da je organsko vezivanje I- u štitnjači belog pacova blokirano kada koncentracija I_2 plazme dostigne kritično visok prag (200–350 mg / L ili 1,6–2,8 mM). Korišćenjem svežih režnjeva štitaste žlezde pacova, koji daju izvrsnu količinu jodtironina in vitro, inhibitorni efekti na sintezu T3 ili T4 postali su očigledni kada je koncentracija jodida bila veća od 2,5 mM (22). Ova pojava, poznata

kao akutni Wolff-Chaikoff-ov efekat koji sugerise princip „Previše je loše, kao i premalo”, objašnjena je stvaranjem organskih jodojedinjenja, poput jodoheksadekanala, koji mogu biti uključeni u autoregulacione procese u štitnoj žlezdi (23). Međutim, pokazalo se da su inhibitorni efekti prolazni zbog smanjenja I-transporta izazvanog smanjenom aktivnošću Na^+ / I^- -simportera (24).

Inhibicija organifikacije jodida može delimično objasniti klinički efekat viška jodida na Gravesovu hipertireozu (25, 26). Međutim, efekat jodida na smanjenje nivoa serumskog tiroksina u Graves-ovoj hipertireozu javlja se ranije nego kod primene terapije tionamidima (1, 27). Sugerisano je da, za razliku od tionamida, višak jodida utiče na gotovo sve važne aspekte metabolizma joda u štitastoj žlezdi, uključujući ne samo organifikaciju joda, već i stvaranje cAMP, vaskularnost, transport jodida, konjugaciju i sekreciju tiroksina (27, 28). Štaviše, nekroza humanih epitelnih ćelija štitaste žlezde indukovana je u prisustvu više od 10 mM KI (29).

Nije jasno zašto se izmicanje od efekta viška jodida često primećuje kod nelečenih pacijenata sa Graves hipertireozom uprkos povećanom unosu jodida (25, 26), dok je jodidom indukovana hipotireoza česta kod hroničnog tiroiditisa (30–32) i zračenih ili operisanih pacijenata sa Gravesovim hipertiroidizmom (13).

Rezultati studije Okamura i saradnika su pokazali da su neki od pacijenata sa Gravesovim hipertiroidizmom takođe osetljivi na suprafiziološke koncentracije jodida, a samo jodidna terapija bila je efikasna kod 66% pacijenata koji su pokazali neželjene efekte na tionamidne lekove nakon povećanja doze KI na više od 100 mg dnevno. Zanimljivo je da je smanjenje aktivnosti TBII i smanjenje gušavosti, što je rezultiralo remisijom, primećeno kod 38,6% nakon 5–23 godine terapije jodidom. Kontroverzno je pitanje da li tionamidni lekovi imaju imunosupresivne efekte (33). Rezultati Okamuraine studije, zajedno sa nalazima izveštaja o smanjenju TBII nakon terapije perhloratom (34), nisu u skladu sa konceptom direktnih imunosupresivnih efekata tionamidnih lekova. Iako je pokazano da su životinje sa nedostatkom joda bile vrlo osetljive na Wolff-Chaikoff efekat (35), mehanizmi u osnovi razlika u osetljivosti na višak jodida u oblastima koje su jod-suficijentne su nepoznati (25). Uzimajući u obzir procenjeni sadržaj joda u štitastoj žlezdi i ukupnog telesnog joda od 10, odnosno 15 mg (36), potrebna je velika količina jodida da bi se održao dovoljan sadržaj intratiroidnog joda za suzbijanje funkcije štitne žlezde, moguće pasivnim I-transportom.

Potrebne su dalje studije kako bi se utvrdili načini predviđanja odgovora pacijenata na KI terapiju. Međutim, remisija je primećena kod 70,8% pacijenata čije je stanje kontrolisano sa manje od 200 mg KI, u poređenju sa samo 35,0% pacijenata kojima je bilo potrebno 200 mg ili više KI, što sugerise da je šansa za remisiju mala kod pacijenata neosetljivih na KI.

Prednost KI terapije je što su njeni efekti reverzibilni, bez ozbiljnih neželjenih efekata, poput leukocitopenije ili oštećenja jetre. Indukcija hipotiroidizma (13, 18, 30–32) ili prolazno povećanje aktivnosti TBII (20) mogu odražavati morfološke (29),

hemijske (32) ili imunološke (31) perturbacije u štitastoj žlezdi izazvane jodidom. Budući da smanjenje doze KI može izazvati pogoršanje tirotoksikoze kod Gravesovog hipertiroidizma, pacijenti su lečeni kombinovanom terapijom koja sadrži KI i sintetički L-tiroksin. Do sada nisu pronađeni nikakvi dokazi da je višak jodida uticao na organe bez Na⁺ / I⁻ simportera, ali su potrebne dalje studije kako bi se procenila bezbednost hronične KI terapije. Postoje spekulacije da je smanjena količina jodidnih jona u ćelijama štitaste žlezde direktan podsticaj ćelijske aktivnosti (38). Tireociti u difuznoj toksičnoj strumi mogu se ponašati kao da im nedostaje joda, a zapravo nisu jod-deficijentne. Ingbar (38) je predložio hipotezu o autoregulaciji štitaste žlezde, koja sugerise da se manifestacije Gravesove bolesti mogu odraziti, barem delimično, na žlezdu koja je izgubila sposobnost da oseti sopstveni sadržaj joda i otuda aktivira mehanizme autoregulacije koji moduliraju funkciju i rast štitne žlezde – takozvano resetovanje štitaste žlezde, jodostat. Studija Okamurae i saradnika sugerise da farmakološke doze jodida mogu da preusmere mnoge funkcionalne, anatomske (verovatno putem involucije) (39) i imunološke abnormalnosti difuznih toksičnih struma nakon dugog kliničkog toka kada je hiperplazija štitne žlezde blaga ili reverzibilna, što rezultira stanjem sličnim spontanoj remisiji. Nakon analize japanske studije, mora se naglasiti da, ako su pacijenti preferirali KI terapiju nakon što su pokazali neželjene efekte na tionamid, bila je potrebna kontinuirana primena velike količine KI do remisije, te da je bila potrebna brza ponovna procena lečenja kada je došlo do izmicanja ili kada je lečenje duže od 3 meseca zahtevalo više od 200 mg KI dnevno.

Perhlorat je anorganski anjon koji je moćan kompetitivni inhibitor natrijum-jodid-simportera (NIS) na bazolateralnoj membrani tiroidnih ćelija. U farmakološkim dozama, perhlorat smanjuje aktivni transport joda u štitastu žlezdu. Tokom 1950-ih, perhlorat (u velikim dozama 600–1000 mg dnevno) korišćen je za lečenje hipertireoze. Njegova upotreba se smanjila nakon što je primećeno nekoliko slučajeva aplastične anemije. Početkom 1980-ih, perhlorat u dozi do 900 mg dnevno korišćen je u terapijskim protokolima za lečenje Graves-ove bolesti bez ozbiljnih neželjenih efekata (41). Poslednjih decenija niže doze se koriste sigurno i efikasno u lečenju Gravesove bolesti i jodom indukovanoj hipertiroidizmi (42). NIS je identifikovan na molekularnom nivou i nekih ekstratireoidnih tkiva, poput mlečne žlezde u laktaciji (gde bi koncentrovanje joda bilo korisno za novorođenče), pljuvačnih žlezda i želuca i crevnih sluznica, u kojima su fiziološke funkcije transporta jodida još uvek nepotpuno rasvetljene (43).

Terapijska razmena plazme (TPE) je vantelesna tehnika prečišćavanja krvi dizajnirana za uklanjanje supstanci velike molekularne težine vezanih za proteine plazme (patogena auto-antitela, imunokompleksi, krioglobulini, mijelomični laki lanci, endotoksini, holesterol koji sadrže lipoproteini i tiroidni hormoni). Indikacije za aferezu samo za tireotoksikozu utvrdilo je Američko društvo za aferezu u okviru kategorije III (44). Kategorija III preporučuje da su dosadašnje procene bile neadekvatne i da je odluka o ovom terapijskom modalitetu individualna. Efikasnost lečenja zavisi od

volumena krvi koja se obrađuje, zapremine plazme koja se razmenjuje u svakom procesu, broj izvedenih procedura, učestalosti razmene i brzine mobilizacije, stabilizacije i ponovne sinteze ćelija ili komponenti plazme (45,46). Kao i svaki invazivni postupak, TPE takođe ima komplikacije. Krvarenja, hematomi i / ili infekcije se povezuju sa upotrebom katetera, kao i poremećaji koagulacije, hipokalcemija, hipotenzija, transfuzione reakcije, bolesti koje se prenose transfuzijom, plućni edem i / ili plućna embolija. Albumin ili sveže smrznuta plazma (FFP) koriste se kao zamena tečnosti u TPE u terapiji tireotoksičnih bolesnika (45, 46). Kroz prizmu literature i na osnovu iskustava Odeljenja za oboljenja štitaste žlezde KCS, TPE je efikasan alternativni tretman koji daje mogućnost pripreme pacijenata za definitivno lečenje: ablativnu terapiju poput RAI ablacije ili tireoidektomiju. Terapijska plazmafereza, ako se izvodi u specijalističkim centrima, sigurna je, brza i efikasna metoda.

Zaključak

Postoje tri osnovna modaliteta za lečenje tireotoksikoze: medikamentna terapija tireosupresivima, ablacija radioaktivnim jodom i hirurško lečenje. Pacijenti kod kojih se ne postigne adekvatna kontrola tirotoksikoze imaju visok mortalitet usled mogućnosti razvoja tiroidne oluje. Primena medikamentne terapije hipertireoze, kao prve linija lečenja, udružena je sa pojavom različitih neželjenih efekata. Neželjeni efekti Metimazola su dozno zavisni, dok u slučaju primene Propiltiouracila nastanak neželjenih efekata nije jasno zavisno od doze. U slučaju opisane pacijentkinje bili su primenjeni svi alternativni, manje poznati modaliteti lečenja hipertireoze, nakon pojave neželjenih reakcija na tireosupresivnu terapiju. Natrijum-perhlorat, tj. natrijumova so perhlorne kiseline se retko koristi u lečenju hipertireoidizma, kao u slučajevima teških idiosinkratičnih reakcija na tionamide, agranulocitoze, hepatitisa, ako nije postignuto eumetabolično stanje i nije moguća aplikacija terapijske doze radijoda. Primenjuje se u vidu rastvora, najčešće 8%. U težim oblicima bolesti, kada je hipertireoidizam veoma izražen, daje se 4 do 6 puta po 10 do 15 kapi dnevno i doza se smanjuje nekada do minimalne doze održavanja. Terapijska razmena plazme (TPE) je vantelesna tehnika prečišćavanja krvi dizajnirana za uklanjanje supstanci velike molekularne težine vezanih za proteine plazme (patogena auto-antitela, imunokompleksi, krioglobulini, mijelomični laki lanci, endotoksini, holesterol koji sadrže lipoproteini i tiroidni hormoni). Efikasnost lečenja zavisi od volumena krvi koja se obrađuje, zapremine plazme koja se razmenjuje u svakom procesu, broja izvedenih procedura, učestalosti razmene i brzine mobilizacije, stabilizacije i ponovne sinteze ćelija ili komponenti plazme. TPE je efikasan alternativni tretman koji daje mogućnost pripreme pacijenata za definitivno lečenje, kod kojih drugim terapijskim modalitetima, kao kod prikazane pacijentkinje, nije moguće uspostaviti adekvatnu metaboličku kontrolu: ablativnu terapiju poput RAI ablacije ili tireoidektomiju. Terapijska plazmafereza, ako se izvodi u specijalističkim centrima, sigurna je, brza i efikasna metoda.

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TAKING ALL THE SIDEROADS OF HYPERTHYROIDISM THERAPY – PITFALLS AND POSSIBILITIES

Abstract: There are three basic modalities for the treatment of thyrotoxicosis: thyrosuppressive drug therapy, ablation with radioactive iodine and surgical treatment. Patients who do not achieve adequate thyrotoxicosis control, as was the case of described patient, have a high mortality rate due to the possibility of developing a thyroid storm. The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects, as was the case in our patient. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. In the case of the described patient, all alternative, lesser known modalities for the treatment of hyperthyroidism were applied, after the occurrence of adverse reactions to thyrosuppressive therapy. Sodium perchlorate, ie. Sodium with perchloric acid is rarely used in the treatment of hyperthyroidism, as in cases of severe idiosyncratic reactions to thionamides, agranulocytosis or hepatitis, if the eumetabolic state is not achieved and the application of a therapeutic dose of radioiodine is not possible. It is applied in the form of a solution, usually 8%; In more severe forms of the disease, when hyperthyroidism is very pronounced, 10 to 15 drops a day are given 4 to 6 times and the dose is sometimes reduced to the minimum maintenance dose. After the adverse reaction even to sodium perchlorate therapy we were left with one more, last option- Plasma Therapy exchange. Plasma Therapy Exchange (TPE) is an out-of-body blood purification technique designed to remove high-molecular-weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myeloma light chains, endotoxins, lipoprotein-containing cholesterol, and thyroid). The effectiveness of treatment depends on the volume of

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blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components. TPE is an effective alternative treatment that provides an opportunity to prepare patients for definitive treatment: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

Key words: Hyperthyreosis, drug adverse effects, Potassium iodine, Sodium perchlorate, Plasma Exchange therapy

Case report

Patient AJ, 36 years old, complains of weight loss, malaise, nervousness, insomnia, sweating, trembling hands, absence of menstruation. Hyperthyroidism was diagnosed in June 2019, when Tiastat was introduced into therapy, after which changes in the skin characteristics of urticaria occurred, and the drug was replaced by Propylthiouracil (PTU). Shortly after the introduction of the drug, there was scratching in the throat, skin manifestations of the erythema type, she noticed that her whites were yellowed. Drug induced hepatitis was diagnosed, after which the therapy was stopped, and the liver enzymes soon returned to normal. In her personal anamnesis, she states a pollen allergy, is a smoker. Family anamnesis is without peculiarities. The patient is conscious, well oriented, TT 62 kg, TV171 cm, BMI 21 kg / m², afebrile, at rest eupnoic, acyanotic, neatly colored, velvety, sweaty skin, neatly hydrated, without peripheral lymphadenopathy, pronounced efflorescences and signs of hemorrhagic syndrome. Neck: cylindrical, actively and passively movable. The veins of the neck are inconspicuous. Thyroid gland is enlarged, soft, painfully insensitive to palpation, mobile when swallowing, without palpable nodules and regional lymph nodes. Percussion present sonority, auscultatory normal respiratory sound, without accompanying findings. Heart rate arrhythmic, fr 120 / min, yew tones, TA 100/60 mmHg. ECG: Sinus tachycardia, fr. 24 in min., Without changes in ST segment or T wave. Radiography of the heart and lungs neat. Neck ultrasound: The thyroid gland is laid lower, enlarged, isthmus about 10 mm thick. The parenchyma of the gland is hypoechogenic, homogeneous, with an enhanced CD signal, pseudonodulated. Paratracheal LN are up to 10 mm in diameter. There are no pathologically altered lymph nodes in the jugular chains. Both submandibular and parotid glands have a homogeneous echostructure, without focal changes (TIRADS DL1 LL1). Abdominal ultrasound of normal findings. Thyroid status on admission: Thyrostimulating hormone (TSH): <0.005 mIU / L [0.27 – 4.2], Thyroxine free (fT4): > 100.0 pmol / L [12.0 – 22.0] Triiodothyronine, free (fT3): 44.85 pmol / L [3.1 – 6.8], Antibodies to thyroid peroxidase (anti-TPO):

66.0 IU / L [0.0 – 34.0], Antibodies to thyroglobulin (anti-TG): 632.0 IU / L [0.0 – 115.0] TSH receptor antibodies: 7.0 IU / L.

KJ (Potassium iodide, Lugol's solution), 3 x 7 gtt with Pronisone tbl 20 + 10 mg, was introduced into the therapy. Thyroid status progressively: fT4: 77.8... 60.9... 44.5... 41.3 pmol / L, fT3: 19.33... 13.55... 10.45... 10.41 pmol / L. In the further course of the disease on the 18th day after the introduction of therapy, the effects of KJ elude: FT4 44.4, FT3 22.1 pmol / l. At her own request and responsibility, the patient is discharged to undergo therapy with Na-perchlorate (NaClO₄) at a dose of 4 x 15 gtt, and then 5 x 21 gtt, after which she develops fever, diarrhea and leukocytopenia, as part of the adverse drug reaction. NaClO₄ therapy was discontinued and treatment with high doses of beta-blockers was continued until hospitalization. Immediately after discontinuation of therapy, the discomfort and fever subsided. Radioactive iodine fixation test (RAI) was performed, percentage of fixation after 24 h: 56.4%. A decision was made to treat with radioactive iodine, with prior application of plasmapheresis. Therapeutic Plasma Exchange (TPE) was performed in five cycles, without adverse events, with an adequate response and a decrease in thyroid hormone concentration (FT3> 50 pmol / l... 5.92 mol / l, FT4> 100 pmol / l ... 15.9 pmol / l The patient was referred to the Center for Nuclear Medicine, KCS, where she received radioiodine therapy, after which Pronison tbl 2 x 20 mg was introduced into therapy. The patient was discharged in good general condition, biochemically euthyroid, with therapy: Propranolol tbl 3x60 mg, Pronison tbl 20 + 10 mg, Nolpaza tbl 40 mg, with regular check-ups every 14 days.

The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. Side effects can be divided into "minor" and "major" forms. "Minor" or mild side effects occur with equal representation in both drugs. They include skin changes (usually urticaria or macular rash) that occur in 4-6%, gastrointestinal problems (1-5%), arthralgia (1-5%) and mild transient granulocytopenia with equal representation for both types of drug. Changes in taste and smell, sialadenitis and headaches can also occur very rarely. Mild skin reactions can be resolved by adding antihistamines while thyrostatic therapy is continued. Alternatively, the patient may be switched from one antithyroid drug to another. However, a cross-reaction can exist in about 50%. The onset of arthralgia, although a "minor" side effect, requires immediate discontinuation of the drug, as it can lead to very severe migratory polyarthritis known as "antithyroid arthritis syndrome". Major or severe side effects occur in 0.2-0.5% of treated patients and include polyarthritis, ANCA-positive vasculitis, hepatotoxicity (immunoallergic hepatitis and cholestasis), agranulocytosis, and very rarely thrombocytopenia, aplastic anemia, hypoglycaemia.

During 1993 a possible association of antimyeloperoxidases of antineutrophil cytoplasmic antibodies (MPO-ANCA) with the use of antithyroid drugs has been

reported with the possibility that antibodies to microsomal antigens consisting mainly of thyroid peroxidase may cross-react with MPO. Hepatotoxicity is another severe complication of thyrosuppressive therapy, which occurs in 0.1-0.2% of cases. There are two types of drug hepatotoxicity and these are direct toxicity and idiosyncrasy. Thyrosuppressive drugs lead to liver lesions by type of idiosyncrasy. The onset of the lesion is unpredictable, the response is not dose dependent and can occur at any time during therapy. Extrahepatic hypersensitivity reactions, such as rash, fever, arthralgia, leukocytosis and eosinophilia, exist in a quarter of patients, which together with the course of the disease suggests that these are immune-mediated reactions. Recent results show that in most cases and in idiosyncratic reactions, there is direct hepatotoxicity, but caused by metabolites more often than by intact drugs. The drug or its metabolite binds to the cellular component of the host, creating a hapten, and the immune response to this neoantigen plays a role in the pathogenesis of the liver lesion. Methimazole and Carbimazole cause cholestasis, while Propylthiouracil causes hepatocyte necrosis. Due to the different mechanisms of hepatotoxicity, the use of an alternative antithyroid drug is possible in further treatment. Agranulocytosis is the most serious complication of thyrosuppressive therapy.

The use of stable iodide in the treatment of hyperthyroidism has been known since the era of Von Basedov (1840) and Trousseau (1863) (1-5). Although iodide was used during the 19th and early 20th centuries, this form of therapy was widely accepted following the insightful observations of Neiser (1920), Loevi and Zondek (1921), and Plummer (1923) (1, 4). Namely, Plummer introduced 10 drops of Lugol's solution containing 5% I₂ and 10% potassium iodide (KI) into the therapy, in a dose of approximately 80–320 mg of iodine per day (5). Beginning in the 1930s, Thompson et al (2) reported satisfactory results after giving patients approximately 6 mg of iodine daily in 64% of mild and 10% of severe cases of Graves-Based hyperthyroidism.

However, the medical literature contains plenty of references on the risks of administering iodine substrates to patients with hyperthyroidism. Iodide therapy brought temporary relief, but evasion of its effects worsened the patient's clinical condition (1). Stanburry reported iodine-induced hyperthyroidism in 1998, but as a complication that arose when iodine was given for endemic goiter (6), in addition to a few reports in the non-endemic area (7). Following the introduction of thionamide and radioactive iodine (RI) therapy, iodide has not been used in the medical treatment of hyperthyroidism (1). Following the introduction of assays to determine thyroid hormones and TSH levels, the initial effects of excess iodide (150–456 mg) on lowering serum T₄ levels were confirmed in most studies (8–12). Although persistently elevated T₃ levels and the onset of an "escape" mechanism have been reported after 2–14 weeks (8, 9), some patients have reached euthyroid status and maintained normal T₄ and T₃ levels for several months (8, 9). Interestingly, the mechanisms of inhibitory action of excess iodide on the thyroid gland were elucidated after the use

of iodide became less common for the medical treatment of hyperthyroidism, except for preoperative preparation or in a thyrotoxic crisis. In 1948, Wolff and Chaikoff (21) reported that organic I- binding in the white rat thyroid was blocked when plasma I₂ concentrations reached a critically high threshold (200–350 mg / L or 1.6–2.8 mM). By using fresh rat thyroid lobes giving excellent amounts of iodothyronine in vitro, inhibitory effects on T₃ or T₄ synthesis became apparent when iodide concentrations were greater than 2.5 mM (22). This phenomenon, known as the acute Wolff-Chaikoff effect, which suggests the principle of "Too bad as well as too little", is explained by the formation of organic iodine compounds, such as iodohexadecanal, which can be involved in autoregulatory processes in the thyroid gland (23). However, inhibitory effects have been shown to be transient due to a decrease in I-transport induced by decreased Na⁺ / I-importer activity (24).

Inhibition of iodide organization may partially explain the clinical effect of excess iodide on Graves' hyperthyroidism (25, 26). However, the effect of iodide on the reduction of serum thyroxine levels in Graves' hyperthyroidism occurs earlier than with thionamide therapy (1, 27). It has been suggested that, unlike thionamide, excess iodide affects almost all important aspects of iodine metabolism in the thyroid gland, including not only iodine organization but also cAMP production, vascularity, iodide transport, conjugation, and thyroxine secretion (27, 28). Moreover, necrosis of human thyroid epithelial cells was induced in the presence of more than 10 mM KI (29). It is not clear why evasion of excess iodide is common in untreated patients with Graves' hyperthyroidism despite increased iodide intake (25, 26), while iodide-induced hypothyroidism is common in chronic thyroiditis (30–32) and irradiated or operated patients with Graves' hyperthyroidism. 13).

The results of a study by Okamura et al showed that some patients with Graves' hyperthyroidism were also sensitive to supraphysiological iodide concentrations, and iodide therapy alone was effective in 66% of patients who showed side effects with thionamide drugs after increasing the dose of KI to more than 100 mg. daily. Interestingly, a decrease in TBII activity and a decrease in goiter resulting in remission were observed in 38.6% after 5–23 years of iodide therapy. It is controversial whether thionamide drugs have immunosuppressive effects (33). The results of the Okamura study, together with the findings of a report on the reduction of TBII after perchlorate therapy (34), are not consistent with the concept of direct immunosuppressive effects of thionamide drugs. Although iodine-deficient animals have been shown to be highly sensitive to the Wolff-Chaikoff effect (35), the mechanisms underlying differences in sensitivity to excess iodide in iodine-deficient areas the suffixes are unknown (25). Considering the estimated iodine content of the thyroid gland and total body iodine of 10 and 15 mg, respectively (36), a large amount of iodide is required to maintain a sufficient content of intrathyroid iodine to suppress thyroid function, possibly by passive I-transport.

Further studies are needed to determine ways to predict patient responses to KI therapy. However, remission was observed in 70.8% of patients whose condition was controlled with less than 200 mg of CI, compared with only 35.0% of patients who required 200 mg or more of CI, suggesting that the chance of remission was low in patients insensitive to CI.

The advantage of KI therapy is that its effects are reversible, without serious side effects, such as leukocytopenia or liver damage. Induction of hypothyroidism (13, 18, 30–32) or transient increase in TBII activity (20) may reflect iodide-induced morphological (29), chemical (32) or immunological (31) perturbations in the thyroid gland. Because dose reduction of KI may cause worsening of thyrotoxicosis in Graves' hyperthyroidism, patients were treated with combination therapy containing KI and synthetic L-thyroxine. To date, no evidence has been found that excess iodide affected organs without Na + / I⁻ symporters, but further studies are needed to assess the safety of chronic KI therapy. There is speculation that a reduced amount of iodide ions in thyroid cells is a direct stimulus of cellular activity (38). Thyrocytes in diffuse toxic goiter may behave as if they are iodine deficient, when in fact they are not iodine-deficient. Ingbar (38) proposed the hypothesis of thyroid self-regulation, which suggests that the manifestations of Graves' disease may affect, at least in part, the gland that has lost the ability to sense its own iodine content and hence activates autoregulatory mechanisms that modulate thyroid function and growth. – so-called thyroid reset, iodostat. A study by Okamura et al suggests that pharmacological doses of iodide may redirect many functional, anatomical (probably by involution) (39), and immune abnormalities of diffuse toxic goiter after a long clinical course when thyroid hyperplasia is mild or reversible. Following the analysis of the Japanese study, it must be emphasized that if patients preferred KI therapy after showing side effects with thionamide, continuous administration of a large amount of KI was required until remission, and that a rapid reassessment of treatment was required when evasion occurred. or when treatment for more than 3 months required more than 200 mg of KI per day. Perchlorate is an inorganic anion that is a potent competitive inhibitor of sodium iodide-importer (NIS) on the basolateral membrane of thyroid cells. At pharmacological doses, perchlorate reduces the active transport of iodine in the thyroid gland. During the 1950s, perchlorate (in large doses of 600-1000 mg per day) was used to treat hyperthyroidism. Its use has decreased after several cases of aplastic anemia were noticed. In the early 1980s, perchlorate at doses up to 900 mg per day was used in therapeutic protocols to treat Graves' disease without serious side effects (41). In recent decades, lower doses have been used safely and effectively in the treatment of Graves' disease and iodine-induced hyperthyroidism (42). NIS has also been identified at the molecular level of some extrathyroid tissues, such as the lactating mammary gland (where iodine concentration would be beneficial for the newborn), salivary glands and gastric and intestinal mucosa, in which the physiological functions of iodide transport are still incompletely elucidated (43).

Plasma Therapeutic Exchange (TPE) is an out-of-body blood purification technique designed to remove high molecular weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myeloma light chains, endotoxins, cholesterol-containing lipoproteins and thyroid hormones). Indications for apheresis only for thyrotoxicosis have been established by the American Society for Apheresis within category III (44). Category III recommends that previous assessments have been inadequate and that the decision on this therapeutic modality is individual. The effectiveness of treatment depends on the volume of blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components (45,46). Like any invasive procedure, TPE also has complications.

Bleeding, hematomas and / or infections are associated with catheter use, as well as coagulation disorders, hypocalcaemia, hypotension, transfusion reactions, transfusion-transmitted diseases, pulmonary edema and / or pulmonary embolism. Albumin or fresh frozen plasma (FFP) is used as a fluid replacement in TPE in the treatment of thyrotoxic patients (45, 46). Through the prism of the literature and based on the experience of the KCS Department of Thyroid Diseases, TPE is an effective alternative treatment that provides the opportunity to prepare patients for definitive treatment: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

Conclusion:

There are three basic modalities for the treatment of thyrotoxicosis: drug therapy with thyrosuppressants, ablation with radioactive iodine and surgical treatment. Patients who do not achieve adequate control of thyrotoxicosis have a high mortality due to the possibility of developing a thyroid storm. The use of drug therapy for hyperthyroidism, as the first line of treatment, is associated with the appearance of various side effects, as was the case of presented patient. Side effects of Methimazole are dose-dependent, while in the case of Propylthiouracil, the occurrence of side effects is not clearly dose-dependent. In the case of the described patient, all alternative, lesser known modalities for the treatment of hyperthyroidism were applied, after the appearance of adverse reactions to thyrosuppressive therapy. Sodium perchlorate, ie. Sodium with perchloric acid is rarely used in the treatment of hyperthyroidism, as in cases of severe idiosyncratic reactions to thionamides, agranulocytosis, hepatitis, if the eumetabolic state is not achieved and the application of a therapeutic dose of radioiodine is not possible. It is applied in the form of a solution, usually 8%; In more severe forms of the disease, when hyperthyroidism is very pronounced, 10 to 15 drops a day are given 4 to 6 times and the dose is sometimes reduced to the minimum

maintenance dose. Plasma Therapy (TPE) is an out-of-body blood purification technique designed to remove high molecular weight substances bound to plasma proteins (autoantibody pathogens, immunocomplexes, cryoglobulins, myelomotor-containing endopoxy light chains) and thyroid hormones). The effectiveness of treatment depends on the volume of blood being processed, the volume of plasma exchanged in each process, the number of procedures performed, the frequency of exchange and the rate of mobilization, stabilization and re-synthesis of cells or plasma components. TPE is an effective alternative treatment that enables the preparation of patients for definitive treatment in which other therapeutic modalities, such as the presented patient, cannot establish adequate metabolic control: ablative therapy such as RAI ablation or thyroidectomy. Therapeutic plasmapheresis, if performed in specialist centers, is a safe, fast and effective method.

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