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DEMENCIJA SA LEVIJEVIM TELIMA – PREGLED LITERATURE I PRIKAZ SLUČAJA

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Apstrakt: Demencija sa Levijevim telima (DLT) je treća ili druga po učestalosti degenerativna demencija. Patološki se karakteriše Levijevim telima (LT), intracitoplazmatskim inkluzijama koje imunohistohemijski reaguju sa anti-ubikvitin i anti-alfa-sinuklein antitelima. Opisane su i nasledne forme DLT. Osnovne kliničke karakteristike DLT su progresivna demencija, parkinsonizam akinetsko-rigidnog tipa, ponovljene vizuelne halucinacije i fluktuacije stanja svesti i kognicije. Nekad se javljaju i ponavljani padovi i sinkope, osetljivost na neuroleptike, sistematizovane sumanute ideje, halucinacije u drugim modalitetima čula, depresija, bihevioralni poremećaj REM spavanja, vegetativni znaci, a retko i druga ispoljavanja. Biohemijski je dominantan deficit kortikalne holinergičke inervacije. DLT ima progresivan tok, koji je brži nego kod Alchajmerove bolesti, kao i ubrzan mortalitet. Bolest traje od jedne do dvadeset godina, prosečno šest godina. Neuropsihološki nalaz odgovara kombinaciji kortikalne i subkortikalne demencije, sa najizraženijim poremećajima pažnje, vizuospacijalnih funkcija, radne i semantičke memorije i egzekutivnih funkcija. Diferencijalna dijagnoza obuhvata druge demencije, pre svega Alchajmerovu bolest i ekstrapiramidne bolesti. U terapiji DLT uglavnom se koriste inhibitori holinesteraze. Potrebno je, koliko god je moguće, izbegavati davanje neuroleptika koji mogu da ubrzaju tok bolesti ili, čak, izazovu smrtni ishod. Prikazan je i slučaj bolesnika sa tipičnom DLT, sa tokom od pet godina i svim kliničkim ispoljavanjima koja zadovoljavaju kriterijume za postavljanje ove dijagnoze.

Uvod

Demencija sa Levijevim telima (DLT) po učestalosti je drugi ili treći tip demencije, sa zastupljenošću od 15-20% (1). Patohistološki marker bolesti su intracitoplazmatske inkluzije, nazvane Levijeva tela (LT). DLT se klinički ispoljava demencijom, fluktuacijom kognicije i stanja svesti, akinetskorigidnim parkinsonizmom i neprovociranim ponavljanim vizuelnim i drugim halucinacijama. Pre izdvajanja kao posebnog entiteta DLT je najčešće dijagnostikovana kao Alchajmerova bolest (AB) ili kao Parkinsonova bolest (PB), što su i danas česte dijagnostičke greške.

DLT su prvi put opisali, početkom šezdesetih godina, Okazaki i saradnici (2). Kao poseban entitet prvi su je opisali Kosaka i saradnici (3), ali je tek tokom devedesetih godina prepoznat njen značaj. Moguće je da postoji više kliničkih varijanti ove demencije. Postoje retke porodične pojave, ali genetski defekt nije utvrđen. Zastupljenost vaskularne patologije u DLT iznosi oko 30% (4). Bolest počinje obično između 62 i 74. godine, prosečno sa oko 70 godina (4) i zahvata muškarce nešto više nego žene (5). Terapijski pokušaji nisu do sada doveli do značajnijih uspeha i bolest progredira posle početnih oscilacija do neumitnog letalnog ishoda. Bolest traje od jedne do dvadeset godina, prosečno šest godina (5).

Klinička slika

Ispoljavanja DLT su kognitivna, neurološka i psihijatrijska. Demencija je pretežno kortikalnog tipa, sa preovladavanjem vizuospacijalnih, ali i prefrontalno-subkoritkalnih karakteristika (1). Često je prva smetnja otežano pamćenje, a rano se javljaju i vizuospacijalne i vizuokonstrukcione smetnje (6). Izraženi su deficiti pažnje, naročito selektivne, radne i semantičke memorije, kao i disegzekutivni sindrom (7). Zahvaćene su sve neuropsihološke funkcije. Nešto su očuvaniji, bar u početku, odloženo prisećanje i orijentacija.

Od psihijatrijske simptomatologije u DLT preovlađuju vizuelne halucinacije (46%), akustičke halucinacije (19%) i depresija (38%) (4). Viđaju se i olfaktivne halucinacije iluzije, sumanute ideje i anksioznost. Vizuelne halucinacije se ponavljaju, formirane su i detaljne i najčešće se javljaju u trenucima snižene svesti. One veoma liče na halucinacije kod trovanja antiholinergicima, ili one koje se javljaju u metaboličkim poremećajima (8). Sačinjavaju ih slike ljudi i životinja. Halucinacije se preklapaju sa vizuospacijalnim smetnjama i vizuelnom agnozijom (9). Nađena je pozitivna korelacija vizuelnih halucinacija i LT u donjim temporalnim režnjevima (10). Akustičke halucinacije su ređe ali, kada se jave, tipično su povezane sa vizuelnim (5). Za DLT su karakteristične sumanute ideje usled pogrešnog prepoznavanja, što se objašnjava zahvaćenošću okcipitalne kore i njenih veza. U ranijim fazama bolesnici imaju uvid u patološko poreklo ovih opažanja.

Parkinsonizam u DLT je obično akinetsko-rigidnog tipa. Poremećaji motorike ispoljavaju se kao rigidnost i bradikinezija, blagi su, a mogu da se jave i hipofonija, hipomimija, poremećaji posturalnih refleksa i parkinsoni hod sa izostankom sinkinetskih pokreta ruku. Rigidnost je često aksijalnog tipa. Nije neuobičajen ni tremor, koji može da bude posturalni i/ili u miru, unilateralan, bilateralan, simetričan ili asimetričan. U više od polovine slučajeva na početku bolesti nema parkinsonizma (4). Oko 10% bolesnika do kraja života nema ekstrapiramidne znake, što jako otežava zaživotnu dijagnozu (11). Ponovljeni padovi i sinkope javljaju se kod bolesnika sa većom zahvaćenošću autonomnog nervnog sistema.

Bolesnici sa DLT su veoma osetljivi na dejstvo neuroleptika (61%), i po pravilu se javlja jatrogeni parkinsonizam (4), ali i smrtni ishodi. Postoji i osetljivost na sedative. Poslednjih godina sve više se sagledavaju do sada zapostavljeni poremećaji REM faze spavanja i depresija. Poremećaji REM faze ispoljavaju se kao epizode intenzivnih pokreta ekstremiteta sa vokalizacijama u snu i sa kasnijim prisećanjem sadržaja snova (12).

Demencija, i eventualno motorni deficiti, počinju da ometaju socijalno i profesionalno funkcionisanje rano u toku bolesti (9). Kognitivni pad je brži u DLT nego u AB, a očekivano trajanje bolesti je kraće (13, 14). Tokom bolesti demencija postaje sve teža, rigidnost sve izraženija, da bi na kraju bolesnici bili duboko dementni, u akinetskom mutizmu i kahektični (5). Poslednji stadijum najčešće počinje naglo, sa pogoršanjem konfuznosti, psihotičnih ispoljavanja i ponašanja, uz manje lucidne intervale, da bi ubrzo došlo do smrtnog ishoda, obično usled aspiracione pneumonije (5).

Histopatološke promene

Najčešće patološke promene u DLT su Levijeva tela (LT) prisutna u subkortikalnim oblastima kao i u korteksu, Levijevi neuriti, senilni plakovi (SP), neurofibrilarna klubad (NFK), gubitak neurona i sinapsi, spongiformne promene (mikrovakuolizacija), i kortikalni holinergički deficit (1, 15). LT se prvo javljaju u amigdali, zatim u limbičkoj kori, i na kraju u neokorteksu (16). Kortikalna LT su najvažniji patološki marker DLT (17). LT su obavezna za dijagnozu DLT, dok ostale promene nisu (8). Prisustvo LT je dovoljno za pojavu demencije i bez SP i NFK (18). Pokazano je da alfa-sinuklein sačinjava glavninu filamenata LT i Levijevih neurita, a takođe su prisutni i ubikvitin, torzin-A, protein 14-3-3 i drugi molekuli (19).

Biohemijske promene

Na biohemijskom planu nađeno je sniženje holinergičke aktivnosti u kori, čak izraženije nego u AB (20). Halucinacije su češće kod DLT bolesnika sa nižim nivoom acetilholina (ACh) u moždanoj kori (8). Posebno se smatra značajnom hipofunkcija okcipitalnog režnja. Pojava vizuelnih halucinacija objašnjava se lezijama optičkog puta, koje dovode do izmenjenog

dotoka vizuelnih informacija i njihove patološke obrade, ili se radi o kortikalnom fenomenu oslobađanja (21). Lezije moždanog stabla sa zahvaćenošću ascendentnih holinergičkih i serotoninergičkih puteva takođe mogu da daju halucinacije, ali i poremećaje spavanja (21). Treća uloga niskog ACh vidi se u retikularnim jedrima talamusa, koja primaju holinergička vlakna iz nukleusa bazalisa i pedunkulopontinog jedra. Snižen nivo ACh u ovoj strukturi može da dovede do poremećaja obrade senzorne informacije, što dalje utiče na pažnju i percepciju i može da doprinosi nastanku vizuelnih halucinacija (8). Dokazan je gubitak dopaminergičkih neurona u subkortikalnim jedrima i noradrenergičkih neurona u locus ceruleus-u, kao i gubitak holinergičkih neurona u nucleus basalis Meynert (22). Depresija i psihoza su u DLT uglavnom vezane za promene u noradrenergičkom i serotoninergičkom sistemu (23).

Dijagnostika

Konzorcijum za demenciju sa LT doneo je „konsenzus kriterijume" 1996. godine, koji definišu dijagnozu DLT (9). Dijagnostika mora da obuhvati detaljno somatsko, neurološko, psihijatrijsko i neuropsihološko ispitivanje, kao i uobičajene laboratorijske testove. Magnetna rezonanca mozga pokazuje gubitak moždanog tkiva obostrano, u temporalnim i frontalnim režnjevima, kao i u kori insule, uz očuvanost medijalnog temporalnog režnja, hipokampusa, amigdale i talamusa, što može da posluži u razlikovanju u odnosu na AB (24). Nekad se nalaze i promene u beloj masi hemisfera, posebno u frontalnim režnjevima, paraventrikularno. Mogu da se nađu i hiperintenzne promene u beloj masi kao u VaD i AB (25). Ispitivanje krvnog moždanog protoka i metabolizma glukoze pokazuje deficit u retrorolandičkim oblastima, naročito u okcipitalnoj kori (4). Elektroencefalografija pokazuje većinom generalizovano usporenje osnovne aktivnosti, ili frontalna pražnjenja. Nekad se viđaju oštri talasi u temporalnim režnjevima (5). Postoje značajne oscilacije u okviru 90 sekundi u reakcionom vremenu i u elektroencefalogramu (EEG) koje se menjaju veoma brzo, što govori o promenama na neurohemijskom, a ne na strukturnom nivou.

Diferencijalna dijagnoza

Definitivna dijagnoza DLT ostaje histopatološka. Veoma je važno u svim slučajevima moguće AB ali i VaD misliti i na DLT. U nekim slučajevima ne postoje jasni ekstrapiramidni znaci, nema uočljivih fluktuacija niti halucinacija, pa na DLT može slučajno da ukaže preosetljivost na neuroleptike (11). Ekstrapiramidni znaci mogu da nedostaju u oko 10% do 20% bolesnika sa DLT, a vizuelne halucinacije u čak 54% (11). U DLT preovlađuju sumanute ideje pogrešne identifikacije, a u AB sumanute ideje proganjanja (26).

U PB ekstrapiramidni poremećaji nastaju ranije, a demencija, ako se javi, obično nastaje posle najmanje godinu dana od motornih fenomena. Ukoliko se demencija javi unutar 12 meseci od pojave parkinsonih znakova, treba da se postavi dijagnoza moguće DLT, a ukoliko je trajanje motornih fenomena duže od 12 meseci pre pojave demencije, onda se radi o PB sa demencijom (koja može da bude tipa DLT, ali i ne mora) (9). Važno je da se isključe i slični ekstrapiramidni poremećaji, kao što su progresivna supranuklearna paraliza, kortikobazalna degeneracija i multisistemska atrofija.

Razlika prema grupi frontotemporalnih demencija (FTD) je u manjoj zastupljenosti frontalnih izmena ponašanja (euforija, dezinhibicija) i kognicije kod DLT (26). S druge strane, i kod FTD može da se, kod oko jedne trećine bolesnika, javi preosetljivost na neuroleptike (27). VaD je čest tip demencije, a preklapanja, klinički i patološki, sa DLT nisu retka. Oscilacije u DLT su obično češće i mogu da imaju znatno veću učestalost i amplitudu u kratkom vremenskom intervalu nego u VaD.

Krojcfeld-Jakobson bolest (KJB) je diferencijalno dijagnostička mogućnost kada je tok DLT brz, kada se pojave fokalni neurološki znaci i mioklonizmi. Ovde su nekad od pomoći karakterističan EEG sa repetitivnim oštrim talasima, i pozitivan nalaz proteina 14-3-3 u cerebrospinalnom likvoru koji se javljaju u KJB, ali oni mogu ponekad da se vide i u DLT (28). Mioklonus i rigidnost takođe nisu specifični. Najviše u prilog DLT govore fluktuacije kognicije i pažnje, parkinsonizam i prisustvo smetnji vida, a u prilog KJB ataksija i smetnje vida.

Epizode delirantnih stanja treba da se razlikuju od delirijuma metaboličkog, infektivnog ili drugog porekla, ali uvek treba da se misli i na komorbiditet (4). S obzirom na ranu i čestu pojavu psihijatrijske simptomatologije, neophodno je da se isključe depresija, manija i shizofreniformni poremećaj kasnog početka.

Terapija

S obzirom da još nema etiološke terapije DLT, a postoji širok spektar ispoljavanja na kognitivnom, bihevioralnom i neuropatološkom planu, jasno je da će biti neophodne višestruke terapijske procedure da bi se tok bolesti makar usporio (29). Treba svakako izbeći primenu neuroleptika, koji čak i u malim dozama dovode do značajnog kognitivnog pada i motornih smetnji (30). Zabeleženi su i smrtni ishodi, a kod nekih je klinički tok bio znatno ubrzan, tako da je ukupni mortalitet kod bolesnika sa DLT lečenih klasičnim neurolepticima za 50% veći nego kod nelečenih (5). Ukoliko je neophodno da se psihotični fenomeni farmakološki kontrolišu, mogu kratko da se daju tioridazin od 10 mg dva puta dnevno, sulpirid 100 do 20 0 mg dnevno i lorazepam 1 do 2 mg. Klozapin se daje u dozi od jedne četvrtine tablete od 25 mg pred spavanje, zbog izraženog sedativnog dejstva. Obično su dovoljne

doze manje od 25 mg dnevno. Moguća je i primena drugih atipičnih neuroleptika, ali je i tu prisutan rizik komplikacija.

Antiholinergici izazivaju kod ovih bolesnika pojavu delirijuma (30). U težim slučajevima sa izraženijom parkinsonom simptomatologijom imala je efekta primena levodope (31) i agonista dopamina (5). Daju se male doze, a počinje se sa kombinacijom levodope i benzerazida od 62,5 mg, dva puta dnevno. Doza se oprezno povećava, prema motornim i mentalnim promenama. Opasnost, kako levodope tako i agonista dopamina, je u mogućem izazivanju psihotičnih ispoljavanja (5).

Neke studije ohrabruju u pogledu primene lekova koji pojačavaju holinergičku inervaciju kao što je donepezil (5 mg), za koji je pokazano da utiče naročito na smanjenje halucinacija, ali i poboljšava funkcionalne sposobnosti (32). Studije sa primenom rivastigmina u dozama od 6-12 mg dnevno pokazale su statistički i klinički značajne bihevioralne efekte uz dobru podnošljivost (33). Treba biti veoma oprezan ukoliko se kombinuju inhibitori holinesteraze i antipsihotici zbog povećanog rizika od nastajanja neželjenih dejstava. Kod depresije mogu da se primene selektivni inhibitori preuzimanja serotonina (34).

Prikaz slučaja

Bolesnik J. B., visokoobrazovani muškarac, rođen 1923. godine. Od pedesete godine života je bolovao od srca, sa apsolutnom aritmijom i kardiomiopatijom. Takođe je bolovao od lumboishialgije, imao je kontrakturu desnog ramena posle frakture, i šećernu bolest koja je lečena samo dijetom. Prve smetnje iz neurološkog domena počinju 1990. godine, sa podrhtavanjem ruku. Tokom 1993. godine javila se hipofonija, i promena rukopisa koji je postao manje čitljiv. Iste godine supruga je primetila da su mu pojedine reakcije „detinjaste". Neurološki nalaz početkom juna 1994. godine pokazao je neiscrpljiv glabelarni refleks, hipomimiju, lak rigor i tremor u miru desne ruke, hipokinezu obostrano, obostrani izostanak sinkinetskih pokreta mahanja rukama, i lako ukočen stav tela. Zbog suspektnog parkinsonizma dobio je da pije selegilin i tokoferol. Krajem istog meseca počele su vizuelne halucinacije, postao je agresivan braneći se od „Nemaca". Istovremena pojava vidnih i slušnih halucinacija zabeležena je 5. avgusta 1994. godine. Prvo je imao slike koje je opisivao kao u „Mapet šou", a zatim mu se činilo kao da ga neko napada i branio se, prepoznajući pogrešno i osobe iz okoline. Smetnje su trajale oko devet dana i stanje se postepeno popravilo. Selegilin je doveo do redukcije tremora i bolje pokretljivosti, ali je zbog psihičkih smetnji ukinut. Neurološki nalaz je bio nepromenjen. Neko vreme nije imao vizuelne halucinacije. Krajem avgusta dobio je ponovo da pije selegilin. Postepeno je sve teže obavljao toaletu, te je supruga morala da mu pomaže sve više. Ispoljavao je anksioznost, a posebno strah od smrti. Od marta 1995. godine ponovo su se javile vizuelne halucinacije. Povremeno su imale i ekstrakampni karakter, te mu se činilo da mu neko stoji iza leđa, a imao je i jednu epizodu derealizacije. Epizode su se javljale sa različitom učestalošću, i trajale i više sati ili dana. U ovom periodu imao je uvid u neprirodni karakter ovih vizuelnih pojava. Nije više imao strah. Neurološki nalaz od kraja marta 1995. godine pokazao je laku usporenost, teže oblačenje, manuelnu nespretnost u svim aktivnostima; tremor, rigor i akineza bili su dis-kretnog stepena. Leva nazolabijalna brazda je bila plića, leva ruka je blago pronirala, a mišićni refleksi na istezanje bili su uslužniji levo. Neurobihevioralna procena pokazala

je teškoće u nabrajanju meseci unazad, kopiranju crteža, zatim diskalkuliju, apraksiju poze, dok je govor bio očuvan. Pamtio je dve od tri zadate reči. Dinamička praksija bila je očuvana. Postavljena je dijagnoza parkinsonizma, demencije i blage levostrane hemipareze, verovatno vaskulnog karaktera. Dobio je da pije pentoksifilin tablete. U aprilu su se javili fenomeni derealizacije, kada povremeno nije prepoznavao svoju kuću, kao i periodi uznemirenosti i lutanja. Krajem juna bio je veoma zabrinut zbog bolesnih pojava koje su mu se javljale i pominjao da bi se ubio jer je nepravedno optužio svoju ženu da je „veštica". Početkom jula ponovo vidi nepostojeće osobe, svađa se sa njima, tera ih iz kuće. Halucinacije su u tom periodu učestale. U rečniku je ponekad počeo da koristi i po neku vulgarnu reč, što ranije nije činio. Jedna od tih epizoda se zbila drugog jula, kada je izbo nožem stvari po kući braneći se od „Švaba" i nasrnuo na prijatelja koji je došao u posetu, ne prepoznavši ga. Odveden je u psihijatrijsku bolnicu, gde je dobio 10 mg dijazepama muskularno, i potom bio vraćen kući. Sledećeg dana se ponovila slična situacija, ispreturao je stvari po kući braneći se od „neprijatelja". Toga dana je hospitalizovan u psihijatrijskoj bolnici, gde je došlo do srčane dekompenzacije, te je prebačen na kardiološko odeljenje. Nema podataka o eventualnoj neuroleptičkoj terapiji. Posle nekoliko dana došlo je do znatnog povišenja temperature, prebačen je na pulmologiju 17. jula 1995. godine. Klinički je konstatovana bilateralna bronhopneumonija, hronična dekompenzovana miokardiopatija, tahiaritmija apsoluta, somnolencija, uvećanje jetre za dva prsta, povišene transaminaze i urea. Lečen je intenzivno oksigenoterapijom, antibioticima, bronhodilatatorima, kardiotonicima, diureticima i infuzionim rastvorima, ali bez efekta. Bolesnik je umro 19. jula 1995. godine.

DISKUSIJA

Početak bolesti u opisanom slučaju bio je postepen, maskiran mnogim somatskim smetnjama, pre svega vaskulnim. Udeo vaskulnih promena u DLT prisutan je u oko jedne trećine bolesnika (4). Ovome u prilog govori i pri kraju bolesti nađena levostrana hemipareza. Neurološke smetnje su kod našeg bolesnika nastale u 67. godini života, što je životno doba kada nastaje većina neurodegenerativnih oboljenja sa demencijom. Prvi uočeni simptom bio je blagi tremor ruku u miru, što se viđa kod PB, ali i kod DLT (35). Posle oko tri godine primećeni su i akineza i rigor, hipofonija i nečitak rukopis, zajedno sa izmenama ponašanja, a potom i ponavljane vizuelne halucinacije, što su dve od tri osnovne dodatne komponente ispo-ljavanja DLT prema konsenzus kriterijumima (spontano nastali ekstrapiramidni akinetsko-rigidni sindrom i vizuelne halucinacije) (9). Nekoliko meseci kasnije, imao je u jednoj epizodi zajedno vizuelne i akustičke halucinacije i bio agresivan braneći se od umišljenih napada. Video je ljude i živo-tinje, slike su bile žive i elaborisane, što su karakteristike vizuelnih halucinacija u DLT. Pojava akustičkih halucinacija je u DLT ređa, ali, kada se javi, tipično je povezana sa vizuelnim, kao što se ispoljilo i kod našeg bolesnika (5). Opisuju se dosta često i sumanute ideje. Zbog psihotičnih ispoljavanja prekinuto je davanje selegilina, za koji se zna da može da kod osetljivih bolesnika provocira delirantna stanja (5). Sve vreme nisu zapaženi znatniji kognitivni deficiti, mada formalno tada nije testiran, jer je imao očuvanu „fasadu" ličnosti. Indirektan dokaz nastupanja kognitivnih smetnji je da su teškoće u svakodnevnim

aktivnostima postale tako izražene da je supruga morala da mu pomaže. Postajao je sve anksiozniji, ispoljavao strah od smrti, a imao je i depresivna ispoljavanja. Neurobihevioralna procena na oko pet godina od početka bolesti pokazala je smetnje pažnje, vizuospacijalnih funkcija, kalkulije, praksije poze i, u manjoj meri, odloženog verbalnog prisećanja, uz očuvan govor, što odgovara profilu DLT (1). Postavljena je dijagnoza parkinsonizma sa demencijom, što je jedna od dve tipične dijagnostičke greške (uz AB), i verovatni vaskulni akcident sa levostranom hemiparezom. Jedan od ekskluzionih kriterijuma u konsenzus dijagnostičkim kriterijumima su i fokalni neurološki nalazi, ali je danas jasno priznata česta vaskulna komponenta u DLT (4, 9). Tada je, praktično pet godina od početka bolesti, prvi put i primećen kognitivni pad.

Opisivani su slučajevi difuzne bolesti LT bez demencije, kao i početak demencije posle više od godinu dana posle ekstrapiramidne simptomatologije. Neuropsihološko testiranje nije urađeno, ali je verovatno da bi ono u ranoj fazi pokazalo kognitivni pad, jer su nastale znatne smetnje u svakodnevnom funkcionisanju, koje se obično javljaju u kasnijoj fazi demencije. Dalja deterioracija ličnosti ispoljila se dezinhibicijom u govoru, sa upotrebom psovki. U završnom periodu bolesti halucinacije su učestale, bolesnik je bivao sve agresivniji, verbalno, ali i fizički napadajući fiktivne neprijatelje. Svakako da fluktuacije stanja, sa sve češćim delirantnim ispoljavanjima označavaju, kao i sve izraženija demencija i deterioracija ličnosti, ubrzanje toka bolesti. Procena fluktuacija i njihove učestalosti i intenziteta nije još zadovoljavajuće rešena (35). Ovo je jedan od razloga što se dijagnoza DLT još uvek ređe postavlja, jer se na fluktuacije svesti i kognicije ređe misli, a teško ih je i proceniti. Ovi bolesnici po pravilu umiru od pneumonije, što je bio slučaj i sa našim bolesnikom. Ovome je prethodila psihijatrijska hospitalizacija zbog agresivnosti i sumanutih ideja, ali, na žalost, nedostaju podaci o primenjenoj medikamentnoj terapiji, sem dijazepama. Jedna od najvažnijih i praktično najznačajnijih karakteristika DLT je preosetljivost na neuroleptike, ali i benzodijazepine, sa potencijalno fatalnim ishodom (5). Tok bolesti je dosta tipičan za DLT. Bolest je trajala pet godina. Prosečno trajanje DLT je oko šest godina (5). Karakterističan je i završni delirijum, u toku koga mnogi ovakvi bolesnici i umiru.

Prema važećim dijagnostičkim kriterijumima (9), naš bolesnik je ispunjavao uslove za verovatnu DLT, odnosno, postojala je demencija koja se progresivno pogoršavala sa smetnjama pažnje i vizuospacijalnih sposobnosti, a sa relativno očuvanim pamćenjem i govorom, spontano nastali parkinsonizam, elaborisane i ponavljane vizuelne halucinacije i jasne oscilacije u stanju svesti i kognicije koje su trajale različito, ali često po nekoliko dana. U prilog DLT govore i sumanute ideje proganjanja i pogrešnog prepoznavanja i slušne halucinacije, koje su sekundarni dijagnostički kriterijumi. Psihijatrijska simptomatologija kod mnogih bolesnika sa DLT dolazi bar u nekom periodu u

prvi plan. Prisustvo vaskulne komponente, odnosno, fokalnih nalaza je prema kriterijumima znak manje verovatnoće DLT. Međutim, ovo je bolesnik koji je godinama imao vaskulne faktore rizika, a fokalni nalaz se javio tek u poslednjoj godini njegove bolesti, tako da ovo ne može bitno da utiče na dijagnozu DLT koja i inače kod oko jedne trećine bolesnika ima i vaskulne promene mozga. Kod našeg bolesnika nije primenjen ceo repertoar terapije DLT, jer pre pet godina mnogi od aktuelnih lekova nisu bili na raspolaganju. Međutim, savremene studije ne pokazuju baš ohrabrujuće rezultate ni uz terapiju.

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LEWY BODY DEMENTIA – LITERATURE REVIEW AND A CASE STUDY

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Abstract: The Lewy body dementia (LBD) is the second or the third most frequent degenerative dementia. Pathological characteristics of LBD are the Lewy bodies (LB), intracytoplasmatic inclusions that react immunohistochemically with anti-ubiquitin and anti-alpha-synuclein antibodies. Hereditary forms of LBD are also described. The basic clinical characteristics of LBD are progressive dementia, akinetic-rigid parkinsonism, repeated visual hallucinations and fluctuations of the state of consciousness and cognition. Repeated falls and syncopes may occur as well, together with hypersensitivity to neuroleptics, systematic delusional ideas, hallucinations of the other senses, depression, behavioral disturbance of REM sleep, vegetative signs, and, though rarely, other manifestations. Dominant feature on the biochemical level is the deficit of cortical cholinergic innervation. LBD has a progressive course, more rapid than Alzheimer's disease, and faster mortality. The disease lasts 1 to 20 years, the mean length being 6 years. Neuropsychological finding corresponds to the combination of cortical and subcortical dementia, with marked disturbances of attention, visuo-spatial functions, working and semantic memory and executive functions. Differential diagnosis includes other dementias, primarily the Alzheimer's disease and extrapyramidal diseases. In the treatment of LBD, cholinesterase inhibitors are mostly used. It is necessary to avoid administration of neuroleptics as long as possible, since they can accelerate the course of the disease or even cause death. A case is also presented, of a patient with typical LBD that lasted 5 years, with all the clinical manifestations meeting the consensus guidelines for setting the diagnosis of LBD.

INTRODUCTION

The Lewy body dementia (LBD) is the second or the third most frequent type of dementia, with the prevalence of 15-20% (1). Pathohistological markers of the disease are intracytoplasmatic inclusions called the Lewy bodies (LB). LBD is clinically manifested as dementia, fluctuation of cognition and state of consciousness, akinetic-rigid parkinsonism and unprovoked repeated visual and other hallucinations. Before being recognized as a separate entity, LBD was most often diagnosed as Alzheimer's disease (AD) or Parkinson disease (PD), which are still frequent mistakes in diagnosis.

LBD was first described in the early sixties by Okazaki et al. (2). As a separate entity, it was first described by Kosaka et al. (3), but its importance was acknowledged only in the nineties. There may be several clinical variants of this type of dementia. There are seldom familial occurrences, but genetic defect is not determined. The prevalence of vascular pathology in LBD is approximately 30% (4). Onset of the disease is usually between the age of 62 and 74, the mean age of onset being 70 (4), and it is slightly more frequent in males than in females (5). So far, the attempts of therapy did not bring any significant results and the disease progresses after the starting oscillations to the inevitable fatal outcome. The disease lasts from 1 to 20 years, 6 years in average (5).

Clinical picture

The manifestations of LBD are cognitive, neurological and psychiatric. Dementia is predominantly of the cortical type, with the predominant visuo-spatial, but also prefrontal-subcortical characteristics (1). Memory deficits are often the first disturbances to occur, and visuo-spatial and visuo-constructial disturbances occur early as well (6). Attention deficits are manifested, especially in selective, working and semantic memory, as well as the dysexecutive syndrome (7). All the neuropsychological functions are affected. Slightly better preserved, at least in the beginning, are delayed recollection and orientation.

Predominant psychiatric symptoms in LBD are visual hallucinations (46%), acoustic hallucinations (19%) and depression (38%) (4). Olfactory hallucinations, illusions, delusional ideas and anxiety are manifested as well. Visual hallucinations are repeated, they are well formed and detailed, and most often occur in moments of reduced consciousness. They are very similar to the hallucinations due to anticholinergics intoxication or metabolic disorders (8). They consist of images of people and animals. The hallucinations overlap with visuo-spatial disturbances and visual agnosia (9). Positive correlation between visual hallucinations and LB in the lower temporal lobes has been found (10). Acoustic hallucinations are not as frequent, but when they do occur, they are typically connected with visual hallucinations (5). LBD is characterized by delusional ideas due to false recognition, which is ex-

plained by the occipital lobe and its connections being affected by the disease. In the early phases, the patients are aware of pathological origin of these phenomena.

Parkinsonism in LBD is usually of the akinetic-rigid type. Motor skill disorders are moderate and manifested as rigidity and bradykinesia; hypophonia, hypomimia, postural reflexes disorders and parkinsonian gait with the loss of synkinetic movements of the arms may also occur. Rigidity is often axial. Tremor is not unusual either, and it can be postural and/or in rest, unilateral, bilateral, symmetrical or asymmetrical. At the onset of the disease, parkinsonism is not manifested in more than half of the cases (4). Approximately 10% of the patients do not show extrapyramidal symptoms until the end of their life, which makes the life-time diagnosis very difficult to make (11). Repeated falls and syncopes are characteristic for the patients with the more affected autonomic nervous system.

LBD patients are highly sensitive to the effect of neuroleptics (61%) and the result is, as a rule, iatrogenic parkinsonism (4), but the outcome can be fatal too. Sensitivity to sedatives is also manifested. The last few years, more attention was paid to REM sleep disturbances and depression, which have been neglected so far. REM phase disturbances are manifested as episodes of intensive movements of the extremities with vocalizations in sleep, and later recollection of the content of the dreams (12).

Dementia and possible motor deficits start interfering with the social and professional functioning early in the course of the disease (9). Cognitive loss is faster in LBD than in AD, and the expected length of the disease is shorter (13, 14). In the course of the disease, dementia becomes more severe, rigidity more expressed, so that, in the end, the patients are deeply demented, in akinetic mutism and cachectic (5). Most often, the final stage begins abruptly, with aggravated confusion, psychotic episodes and behavior, with short intervals of lucidity; the fatal outcome follows soon, usually as a result of aspiration pneumonia (5).

Histopathological changes

The pathological changes most often to occur in LBD are the presence of LB in subcortical areas as well as in cortex, Lewy's neurites, senile plaques (SP), neurofibrillary tangles (NFT), loss of neurons and synapses, spongiform changes (microvacuolization) and cortical cholinergic deficit (1,15). LB appear in amygdala first, then in the limbic cortex and finally in neocortex (16). The presence of cortical LB is the most significant pathological marker of LBD (17). LB are essential for diagnosing LBD, while the other changes are not (8). The presence of LB is sufficient for the onset of dementia, even without SP and NFT (18). It has been shown that alpha-synuclein constitutes the main part of LB filaments and Lewy's neurites, with the presence of ubiquitin, torsinA, protein 14-3-3 and other molecules (19).

Biochemical changes

On the biochemical level, the reduction of cholinergic activity in the cortex was discovered, even more prominent than in AD (20). Hallucinations are more frequent with LBD patients with a lower level of acetylcholine (ACh) in the cortex (8). Hypofunction of the occipital lobe is thought to be particularly significant. The phenomenon of visual hallucinations is explained by the lesions of the optic pathway, which bring to the altered flow of visual information and their pathological processing, or it is a case of the cortical release phenomena (21). Lesions of the brainstem, with the ascendant cholinergic and serotonergic pathways affected as well, can be the cause of hallucinations too, but also of sleep disturbances (21). The third role of low ACh is seen in reticular nuclei of the thalamus, which intake the cholinergic filaments from nucleus basalis and peduncular-pontine nucleus. Reduced level of ACh in this structure can lead to disturbances in processing the sensory information, which further influences attention and perception, and can add to the occurrence of visual hallucinations (8). Loss of dopaminergic neurons in subcortical nuclei and noradrenergic neurons in locus ceruleus was proved, as was the loss of cholinergic neurons in nucleus basalis of Meynert (22). Depression and psychosis in LBD are usually connected to the changes in the noradrenergic and serotonergic system (23).

Diagnostics

In 1996 the Consortium on dementia with LB established the consensus guidelines, defining the diagnosis of LBD (9). The diagnostics must include detailed somatic, neurological, psychiatric and neuropsychological examinations, as well as the usual laboratory tests. Magnetic resonance of the brain shows the loss of brain tissue bilaterally in temporal and frontal lobes and in the insular cortex, while medial temporal lobe, hippocampus, amygdala and thalamus are preserved, which may help differentiate it from AD (24). Occasionally, changes are found in the white matter of the hemispheres, especially in the frontal lobes paraventricularly. There may also be hyperintensive changes in the white matter, as is the case with VaD and AD (25). The examination of cerebral circulation and glucose metabolism shows a deficit in the retro-rolandic areas, especially in the occipital lobe (4). Electroencephalography shows a mostly generalized slowing down of basic activity or frontal discharges. Occasionally, sharp waves are seen in temporal lobes (5). There are significant oscillations within 90 seconds in reaction time and in the electroencephalogram (EEG), changing rapidly, which indicates changes in neurochemical, and not in the structural level.

Differential diagnosis

Definitive LBD diagnosis remains histopathological. In all the cases of possible AD, but also of VaD, it is very important to have LBD in mind

as well. In some cases, there are no clear extrapyramidal symptoms, nor obvious fluctuations or hallucinations, so a hypersensitivity to neuroleptics may accidentally point to LBD (11). Extrapyramidal symptoms may be lacking in about 10% to 20% of the LBD patients, and visual hallucinations in up to 54% (11). In LBD, delusions of false recognition are predominant, and in AD the delusions of persecution (26).

In PD, extrapyramidal symptoms are manifested earlier, while dementia, if it occurs, manifests itself at least one year after the motor phenomena. If dementia occurs within 12 months of the parkinsonian symptoms, a diagnosis of possible LBD should be made, and if the motor phenomena lasted more than 12 months before the onset of dementia, it is a case of PD with dementia (which may or may not be of the LBD type) (9). It is also important to rule out similar extrapyramidal disorders, such as progressive supranuclear palsy, corticobasal degeneration and multisystemic atrophy.

The difference as compared with the group of frontotemporal dementias (FTD) is that in LBD the frontal changes of behavior (euphoria, disinhibition) and cognition are less often found (26). On the other hand, about one third of FTD patients can develop hypersensitivity to neuroleptics as well (27). VaD is a frequent type of dementia, and the overlapping with LBD, both clinically and pathologically, is not rare. Oscillations in LBD are usually more often than in VaD, and can have a significantly higher frequency and amplitude in a short time interval.

Creutzfeldt-Jacob disease (CJD) is differentially a diagnostic possibility when the course of LBD is rapid, and when focal neurological symptoms and mioclonia appear. Sometimes, the characteristic EEG with repetitive sharp waves and positive finding of protein 14-3-3 in cerebrospinal fluid, which occur in CJD, can be of assistance, but they can sometimes be seen in LBD as well (28). Mioclonus and rigidity are also nonspecific. What favors LBD the most are the fluctuations of cognition and attention, parkinsonism and lack of sight disturbances, while ataxia and sight disturbances are signs of CJD.

Delirious episodes should be distinguished from a delirium of metabolical, infective and other origin, but comorbidity should always be kept in mind (4). Considering the early and frequent occurrence of psychiatric symptomatology, it is necessary to exclude depression, mania and schizophreniform disorder with late onset.

Therapy

Considering that there is still no etiological therapy for LBD, while, on the other hand, there is a wide range of manifestations on the cognitive, behavioral and neuropathological level, it is clear that multiple therapeutic procedures will be needed to at least slow down the course of illness (29). In

any case, we should avoid the use of neuroleptics, since they, even in small doses, lead to a significant cognitive decline and motor skill disturbances (30). Fatal outcomes have been recorded too, and in some cases the clinical course grew significantly more rapid, so the total mortality of LBD patients treated with classic neuroleptics is higher than the non-treated patients' by 50% (5). In case it is necessary for the psychotic phenomena to be kept under pharmacological control, for a short while, thioridazine 10 mg twice a day, sulpiride 100 to 200 mg daily and lorazepam 1 to 2 mg, may be administered. Clozapine is administered in a dose of one quarter of a 25 mg tablet before bedtime, due to its marked sedative effect. In most cases, doses of less than 25 mg daily are sufficient. It is possible to apply other non-typical neuroleptics too, but the risk of complications is still present.

Anticholinergics cause delirium in LBD patients (30). Less often, in cases with the marked parkinsonian symptomatology, the treatment with levodopa (31) and dopamine agonists (5) was effective. Small doses are given, starting with a combination of levodopa and benzerazide of 62.5 mg twice a day. The dose is increased carefully, according to the motor and mental changes. The danger of using levodopa as well as the dopamine agonists, is the possible triggering of psychotic episodes (5).

There are certain encouraging studies regarding the use of medications that strengthen cholinergic innervation, such as donepezil (5 milligrams), which was proved to have an effect on the reduction of hallucinations, and also improves functional abilities (32). The studies of the use of rivastigmine in the doses of 6–12 mg daily have shown statistically and clinically significant behavioral effects, with the patients' responding well to treatment (33). We should be very careful in case of cholinesterase inhibitors combined with antipsychotics, since they increase the risk of side effects. In the treatment of depression, selective inhibitors of serotonin reuptake can be applied (34).

Case study

The patient J.B., highly educated male, born in 1923. He suffered from a heart condition with absolute arrhythmia and cardiomyopathia since he was 50 years old. He also suffered from lumbar ischialgia, right shoulder contracture following a fracture, and diabetes treated by diet only. The first disturbances on the neurological level began in 1990, with hand tremor. During 1993, occurred hypophonia and changes of handwriting, which became less legible. The same year, his wife noticed that some of his reactions were „childish". Beginning of June 1994, the neurological finding showed inexhaustible glabelar reflex, hypomimia, slight rigor and rest tremor of the right hand, bilateral hypokinesis, loss of synkinetic waving movements of the arms and slightly rigid posture. Due to suspected parkinsonism, he was prescribed selegiline and tocopherol. Later the same month, visual hallucination began; he became aggressive, fighting off „the Germans". Simultaneous occurrence of visual and auditory hallucinations was noted on August 5th 1994. First he had images which he described as in the „Muppet Show", and then it seemed to him as if somebody was attacking him and he was defending himself, failing to recognize even his closest relatives and friends. The disturbances lasted about 9 days and the condition gradually improved. Selegiline

brought about the reduction of tremor and better mobility, but the treatment was discontinued due to psychic disturbances. Neurological findings were unchanged. For a while, there were no visual hallucinations. In late August, selegiline was prescribed again. Gradually, the patient found it more difficult to maintain his toilet by himself and his wife had to start helping him more. He showed anxiety and particularly fear of death. Since March 1995, visual hallucinations started again. Occasionally they had an extracampine character, so it seemed to the patient that someone was standing behind him, and he had an episode of derealization. The episodes occurred with different frequency and lasted for several hours or days. In that period he was aware of the unnatural character of the visual phenomena. He did not feel any fear. Neurological finding end of March 1995 showed a slight slowness, difficulties in getting dressed, manual clumsiness in all activities; tremor, rigidity and akinesis were of discreet degree. Left nasolabial groove was shallower, the left hand prowed mildly, and muscle stretch reflexes were better responding to the left. Neurobehavioral assessment showed difficulties in naming the months backwards, copying a drawing, dyscalculia, postural apraxia, while speech was unaffected. He remembered two out of three given words. Dynamic praxia was preserved. He was diagnosed with parkinsonism, dementia and mild left side hemiparesis, probably of vascular character. He was prescribed pentoxifylline tablets. In April, the derealization phenomena started, when occasionally he could not recognize his own house, and periods of uneasiness and wandering off. In June, he was very worried about the strange phenomena happening to him and mentioned that he would kill himself for wrongly accusing his wife of being a „witch". Beginning of July, he was seeing nonexistent people again, fighting with them, and chasing them out of his house. Hallucinations were frequent in that period. He started using vulgar words, which he had never done before. One of such episodes happened on July 2nd when he stabbed things in the house with a knife, defending himself from „the Germans" and attacked a friend who came to visit him, without recognizing him. He was taken to psychiatric hospital where he was given 10 mg diazepam muscular*ly* and then sent back home. On the following day, a similar situation occurred again; he rummaged the house, fighting off the „enemy". On that day he was hospitalized in a psychiatric institution, where cardiac decompensation occurred, so he was transferred to the cardiology ward. There are no data of a potential therapy with neuroleptics. Several days later his body temperature increased highly and he was transferred to the pulmology department on June 17th 1995. Bilateral bronchopneumonia, chronic decompensated myocardiopathia, tachyarrhythmia absoluta, somnolentia, liver enhancement by two fingers, increased level of transaminase and urea were clinically determined. He was treated intensively with the use of oxigenotherapy, antibiotics, bronchodilatators, cardiotonics, diuretics and infusion solutions, but there was no effect. The patient died on July 19th 1995.

DISCUSSION

In the described case, onset of the disease was gradual, masked by a number of somatic disturbances, most of all vascular. The influence of vascular changes in LBD is present in about one third of the patients (4). In favor of this statement is the left side hemiparesis found by the end of his illness. The patient's neurological disturbances began when he was 67, which is a time of onset for the most neurodegenerative diseases with dementia. The first symptom noticed was a mild rest tremor of the hand, which is seen in PD, but also in LBD (35). About three years later, akinesis and rigor were noticed too, together with hypophonia and illegible handwriting, changes of the behavior, and then repeated visual hallucinations, which are two of the three basic additional components of LBD manifestations, according to the

consensus guidelines (spontaneously developed extrapyramidal akinetic-rigid syndrome and visual hallucinations) (9). Several months later he had an episode with both visual and auditory hallucinations, and acted aggressively, defending himself against imaginary attacks. He saw people and animals, the images were vivid and elaborated, which is characteristic of visual hallucinations in LBD. The phenomenon of auditory hallucinations is less often in LBD, but, when it does occur, it is typically connected with visual hallucinations, as was manifested in our case as well (5). Quite often, delusional ideas are present too. Due to psychotic manifestations, treatment with selegiline, known to be able to provoke delirious states in more sensitive patients, was discontinued (5). In all that time, considerable cognitive deficits were not noticed; however, the patient was not formally tested, since the „façade" of his personality was preserved. Indirect proof of the onset of cognitive disturbances is that his wife had to start helping him in everyday activities, since they became too difficult for him. He became more and more anxious, manifested fear of death, and had depressive episodes. Neurobehavioral assessment five years after the onset of the disease showed disturbances of attention, visuo-spatial functions, calculia, postural praxia and, to a lesser extent, delayed verbal memory, the speech being unaffected, which corresponds with the profile of LBD (1). The diagnosis made was parkinsonism with dementia, which is one of the two typical diagnostic mistakes (the other being AD) and probable vascular accident with left-side hemiparesis. Focal neurological findings is one of the exclusion criteria in the consensus diagnostic guidelines, but frequent vascular component in LBD is clearly admitted today (4, 9). It was then, practically five years after the onset of the disease, when the cognitive loss was first noticed. Cases of diffuse disease LB without dementia were described, as well as the onset of dementia more than one year after the extrapyramidal symptomatology. Neuropsychological testing was not performed, but it would probably have shown cognitive loss in the early phase, since there were significant disturbances in everyday functioning, often to occur in a later phase of dementia. Further personality deterioration manifested itself in speech disinhibition and use of curses. In the final stage of the disease, hallucinations became more frequent and the patient more aggressive, verbally, but also physically, attacking fictive enemies. Fluctuations of condition with more frequent delirious manifestations, together with the advancing dementia and personality deterioration, certainly point to acceleration in the course of the disease. There is still no satisfactory solution to the problem of assessing the fluctuations and their frequency and intensity (35). This is one of the reasons why the diagnosis of LBD is still rarely made, since fluctuations of consciousness and cognition are not often kept in mind, and they are difficult to assess. The patients die of pneumonia by a rule, which was the case with our patient too. It was preceded by psychiatric hospitalization, due to aggressiveness and delusional ideas, but, un-

fortunately, the records of the medications applied are lacking, except for diazepam. One of the most important and practically most significant characteristics of LBD is hypersensitivity to neuroleptics, but also to benzodiazepines with the potentially fatal outcome (5). The course of the disease is quite typical for LBD. The disease lasted 5 years. The mean length of LBD is about 6 years (5). What is also characteristic is the final delirium during which many of the patients die.

According to the valid diagnostic criteria (9), the patient fulfilled the conditions for diagnosing probable LBD, that is, dementia was present, advancing progressively, with the disturbances of attention and visuo-spatial abilities, and with memory and speech relatively preserved, spontaneously developed parkinsonism, elaborated and repeated visual hallucinations and clear oscillations in the state of consciousness and cognition, of different length, but which could often last for days. Also pointing to LBD were delusions of persecution and false recognition, and auditory hallucinations, which represent the secondary diagnostic criteria. In many LBD patients, there is at least one period when the psychiatric symptomatology becomes the most prominent. The presence of vascular component, that is, focal findings, is according to the criteria a sign of lesser probability of LBD. However, this was a patient who had vascular risk factors for years, and focal finding occurred only in the final year of his disease, so this cannot have significant influence to the diagnosis of LBD, especially since about one third of the patients have vascular changes of the brain as well. In the case of our patient, the complete scope of LBD therapy could not be applied, since many currently used medications were not available five years ago. However, recent studies do not show encouraging results even with therapy.

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References

1. McKeith IG. Dementia with Lewy bodies. British J Psychiatry 2002; 180: 144-7.
2. Okazaki H, Lipkin LS, Aronson SM. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. M Neuropathol Exp Neurol 1961; 20: 237-44.
3. Kosaka K, Matsushita M, Oyanagi S, Mehraein P. A clinicopathological study of the „Lewy body disease". Psychiat Neurol Japon 1980; 82: 292-311.

4. McKeith I, O'Brien J. Dementia with Lewy bodies. Aust N Z J Psychiatry 1999; 33: 800-8.
5. Luis CA, Mittenberg W, Gass CS, Duara R. Diffuse Lewy body disease: Clinical, pathological and neuropsychological review. Neuropsychol Rev 1999; 9: 137-50.
6. Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. Pentagon copying is more impaired in dementia with Lewy bodies than in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 70: 483-8.
7. Calderon J, Perry RJ, Erzinclioglu SW, Berrios GE, Dening TR, Hodges JR. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2001; 70: 157-64.
8. Ince PG, Perry EK, Morris CM. Dementia with Lewy bodies. A distinct non-Alzheimer dementia syndrome? Brain Pathology 1998; 8: 299-324.
9. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. Neurology 1996; 47: 1113-24.
10. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain 2002; 125: 391-403.
11. Weiner MF. Dementia associated with Lewy bodies. Arch Neurol 1999; 56: 1441-2.
12. Boeve BF, Silber MH, Ferman TJ, Kokmen E, Smith GE, Ivnik RJ et al. REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease. Neurology 1998; 51: 363-70.
13. Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R, Thal LJ. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 1998; 51: 351-7.
14. Shimomura R, Mori E, Yamashita H, Imamura T, Hirono N, Hashimoto M et al. Cognitive loss in dementia with Lewy bodies and Alzheimer`s disease. Arch Neurol 1998; 55: 1547-52.
15. Lowe J, Dickson D. Pathological diagnostic criteria for dementia associated with cortical Lewy bodies: Review and proposal for a descriptive approach. J Neural Transm Suppl 1997; 51: 111-20.
16. Marui W, Iseki E, Nakai T, Miura S, Kato M, Ueda K, Kosaka K. Progression and staging of Lewy pathology in brains from patients with dementia with Lewy bodies. J Neurol Sci 2002; 195: 153-9.
17. Kosaka K. Diffuse Lewy body disease. Intern Med 1998; 37: 6-10.
18. Uchikado H, Iseki E, Tsuchiya K, Togo T, Katsuse O, Ueda K, Kato M, Kosaka K. Dementia with Lewy bodies showing advanced Lewy pathology but minimal Alzheimer pathology – Lewy pathology causes neuronal loss inducing progressive dementia. Clin Neuropathol 2002; 21: 269-77.
19. Sharma N, Hewett J, Ozelius LJ, Ramesh V, McLean PJ, Breakefield XO, Hyman BT. A Close Association of TorsinA and -Synuclein in Lewy Bodies. A Fluorescence Resonance Energy Transfer Study. Am Journal Pathology. 2001; 159: 339-44.

20. Tiraboschi P, Hansen LA, Alford M, Merdes A, Masliah E, Thal LJ, Corey-Bloom J. Early and widespread cholinergic losses differentiate dementia with Lewy bodies from Alzheimer's disease. Arch Gen Psychiatry 2002; 59: 946-51.
21. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain 1998; 121: 1819-40.
22. Lippa CF, Smith TW, Swearer JM. Alzheimer's disease and Lewy body disease: A comparative clinicopathological study. Ann Neurol 1994; 35: 81-8.
23. Jellinger KA. Morphological substrates of mental dysfunction in Lewy body disease: An update. J Neural Transm Suppl 2000; 59: 185-212.
24. Burton EJ, Karas G, Paling SM, Barber R, Williams ED, Ballard CG, et al. Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. Neuroimage 2002; 17: 618-30.
25. McKeith IG, Perry EK, Perry RH. Report of the second dementia with Lewy body international workshop: diagnosis and treatment. Consortium on Dementia with Lewy Bodies. Neurology 1999; 53: 902-5.
26. Hirono N, Mori E, Tanimukai S, Kazui H, Hashimoto M, Hanihara T, Imamura T. Distinctive neurobehavioral features among neurodegenerative dementias. J Neuropsychiatry Clin Neurosci 1999; 11: 498-503.
27. Pijnenburg YA, Sampson EL, Harvey RJ, Fox NC, Rossor MN. Vulnerability to neuroleptic side effects in frontotemporal lobar degeneration. Int J Geriatr Psychiatry 2003; 18: 67-72.
28. Tschampa HJ, Neumann M, Zerr I, Henkel K, Schröter A, Schulz-Schaeffer WJ et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 2001; 71: 33-9.
29. Lockhart BP, Lestage PJ. Cognition enhancing or neuroprotective compounds for the treatment of cognitive disorders: why? when? which? Exp Gerontol 2003; 38: 119-28.
30. McKeith IG, Galasko D, Wilcock GK, Byrne EJ. Lewy body dementia – diagnosis and treatment. Brit J Psychiat 1995; 167: 709-17.
31. Galasko D, Katzman R, Salmon DP, Hansen L. Clinical and neuropathological findings in Lewy body dementias. Brain Cogn 1996; 31: 166-75.
32. Rojas-Fernandez CH. Successful use of donepezil for the treatment of dementia with Lewy bodies. Ann Pharmacother 2001; 35: 202-5.
33. McKeith I, Del Ser T, Spano PF, Emre M, Wesnes K, Anand R et al. Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. Lancet 2000; 356: 2031-6.
34. Swanberg MM, Cummings JL. Benefit-risk considerations in the treatment of dementia with Lewy bodies. Drug Saf 2002; 25: 511-23.
35. Pavlović DM. Demencije – klinička dijagnoza. Autor, Beograd 2002.