Adrenaloleukodistrofija (ALD) predstavlja bolesti akumulacije masnih kiselina veoma dugih lanaca u tkivima po celom telu. Najčešće pogođena tkiva su mijelin u centralnom nervnom sistemu, kora nadbudrežne žlede i Leidig ćelije u testisima. Klinički, ALD je heterohogeni poremećaj, predstavljajući se sa nekoliko različitih fenotipova, i ne postoji jasan obrazac genotip-fenotip korelacije.

Prikaz slučaja: Pacijent A. A, star 50 godina, u trećoj godini života dijagnostikovan primarni hipokorticizam, od 45. godini života ima težbe: malaksalost, glavobolje, vrtoglavice, zanošenje udesno, noćno umokravljanje, povremena inkotinencija urina. Razgovara sam sa sobom, godinu dana svakodnevno boravi na groblju, povremeno više nekontrolisano a da se kasnije toga ne seća.

Stanje spinocerebelarne ataksije i diskretnog levostranog piramidalnog deficita sa inkotinencijom urina i psihijatrijskim problemima zahtevalo je dodatno ispitivanje. U saradnji sa Klinikom za neurologiju sprovedena dijagnostika. Rezultati ispitivanja su pokazali da pacijent boluje od X-zavisne adrenaloleukodistrofije sa zahvaćenosti centralnog i perifernog nervnog sistema.

ALD genetski je poremećaj koji prenosi majka na sina. Posledica je mutacija u genu ABCD1 smještenom na X hromozomu, što dovodi do nedostatka ili disfunkcije transmembranskog proteina ALDP (prenosi VLCFacyl-CoA estrazu iz citosola u peroksidom i time učestvuje u beta oksidaciji). Metabolički poremećaj se karakteriše narušenom beta oksidacijom masnih kiselina veoma dugih lanaca (C>22), pri čemu se one nagomilavaju u plazmi i tkivima. Akumulacija masnih kiselina veoma dugog lanca deluje toksično jer: ima disruptivni efekat na strukturu, stabilnost i funkciju ćelijske membrane, smanjuje oslobađanje kortizola iz humanih adrenokortikalnih ćelija, destruiše astrocite i oligodendrocite, uzrokuje oksidativni stres i oštećuje proteine, aktivira mikrogliju i apop...
tozu. Narušava sposobnost oligodendrocita i Švanovih ćelija da zadrže aksonalni integritet, što rezultuje oštećenjem aksona.

Zaključak: Kod našeg pacijenta hipokorticizam dijagnostikovan u ranoj životnoj dobi je bio prvi znak bolesti i rana manifestacija X-vezane adrenaloleukodistrofije. Kod pacijenta muškog pola sa hipokorticizmom treba razmotriti i adrenaloleukodistrofiju kao uzrok primarnog hipokorticizma.

**Ključne reči:** adrenaloleukodistrofija, Addisonova bolest, X-vezano recessivno nasleđivanje.

**UVOD**

Adrenaloleukodistrofija je recessivni, vezan za X hromozom, genetski poremećaj izazvan abnormalnošću u ABCD1 gena na X hromozomu. Ovaj poremećaj utiče na belu masu nervnog sistema i koru nadbubrega. Neki oboleli imaju insuficijencije nadbubrežne funkcije, što znači smanjenje lučenja hormona kao što su adrenalin i kortizol, ali i drugih hormona, pa oni imaju poremećaje krvnog pritiska, srčane frekvence, seksualnog razvoja i reprodukcije. Neke, od tih uticaja dovode do ozbiljnih neuroloških problema koji mogu uticati na mentalne funkcije i dovode do invalidnosti i smanjenja životnog veka. ALD je kategorisan u šest tipova na osnovu simptoma i starosti početka bolesti: cerebralnom ALD u detinjstvu, adolescentni tip cerebralne ALD, adrenomijeloneuropatija, cerebralne ALD kod odraslih, izolovana adrenalna insuficijencija i ALD koji se javlja kod žena. ALD je najčešći uzorak leukodistrofija, čini oko polovine svih leukodistrofija. Prevalencija je oko 1 / 20,000–1 / 50.000 porođaja, a većina onih koji su pogođeni su osobe muškog pola. Oko polovine svih žena koje nose abnormalno ABCD1 gen će razviti neke simptome ALD.

Addison-ova bolest je redak poremećaj nadbubrežne žlezde. Većini odraslih obolelih je oko polovine svih leukodistrofija. Prevalencija je oko 1 / 20,000–1 / 50.000 porođaja, a većina onih koji su pogođeni su osobe muškog pola. Oko polovine svih žena koje nose abnormalno ABCD1 gen će razviti neke simptome ALD.

ADDISON-ODRAŠLJE

Konzentracija veoma dugih masnih kiselina (VLFA) u krvnoj plazmi povišen je u 99% muškaraca sa ALD, a u oko 85% žena nosilaca abnormalnog ABCD1 gena. Molekularna testiranja za ABCD1 gen su dostupna i pre svega se koriste za potvrdu dijagnoze ako druga testiranja nisu konačna, potrebno je obezbediti genetsko saveto-
vanje sa članovima porodice i za prenatalnu dijagnostiku. Patološki testovi za funkciju nadbubrega se registruju kod 90% dečaka sa ALD koji imaju neurološke simptome i kod oko 70% muškaraca sa adrenomijeloneuropatijom.

Lečenje se odnosi na supstitutionu terapiju abnormalne adrenalne funkcije. Transplantacija koštane srži bila je uspešna kod pojedinaca koji su dijagnostikovani u ranim fazama ALD. Preporučuje se tretman kod psihologa, pedagoga, fiziотера- пута, urologa, a za porodicu i pomoć stručnih savetnika. Genetsko savetovanje se preporučuje sa obolelim osobama i članovima njihove porodice.

**PRIKAZ SLUČAJA**

Pacijent A. A. star 50 godina, hospitalizovan zbog malaksalosti, glavobolja, vrtoglavica, zanošenjem udesno pri hodu, noćnog umokravanja, povremene in-kotinencije urina. Od drugih tegoba heteroanamnestički se saznaje da razgovara sam sa sobom, godinu dana unazad svakodnevno boravi na groblju, povremeno više nekontrolisano a da se kasnije toga ne seća. Pacijent je u trećoj godini života oboleo od TBC pluća, nakon čega je ubrzo dijagnostikovana i Addisonov-a bolest (na Institutu za majku i dete), gde se kontrolisao do 16. god. od postavljanja dijagnoze Hydrocortizonom 10+10+5 mg 1991. god. (u 28. god), samoinicijativno prekinuo supstitutionu i bio bez terapije 10 godina. U tom periodu se dobro osećao, čak i pored perioda gripa sa febrilnošću (nije bilo malaksalosti, niti je koža potamnela više nego ranije). Terapija ponovo uvedena u decembru 2002. god kada se javio lekaru zbog glavobolja. Koža je tammije prebojena od detinjstva. Od 20. godine kosa se difuzno proređuje. Od 2004. godine ima po-tiljačne glavobolje koje su vremenom spontano prestale. Od istog perioda ima i zanošenje pri hodu uglavnom udesno, naročito pri naglom uspravljanju, ali i bez naglih promena položaja tela. U ličnoj anamnezi: u detinjstvu operacija krajnika. TBC pluća u 3. god. života. U porodičnoj anamnezi: majka je lečena na Klinici za neurologiju 1992. godine (u svojoj 64. godini života) zbog trnjenja u nogama, otezanog i nesigurnog hoda. Dg: Hereditarna spastična parapareza. Tetka, majčina sestra, imala je problema sa hodom koji su se javili oko 40. godine, nema detalja o bolesti. Inače je oženjen, ima dva sina.

Pacijent uobičajene osteomuskularne građe, BMI 19,3kg/cm2, afebrilan, eupno-ičan, acijanotican, anikteričan, difuzno lako tmimije prebojene kože, bukalna sluznica normalno prebojena, gingive diskretno tamnije, palmarne brazde tamnije pigmentisane. Uredno hidriran bez periferne limfoadenopatije i znakova hemoragijskog sindroma. Aktivno pokretan, hod ataksičan. Kosa difuzno proređena, nalaz na plućima uredan. Srčana radnja ritmična, tonovi jasni, šumova nema. TA 110/75mmHg, puls 61/min. Trbuh u ravni grudnog koša palpatorno bolno neosetljiv bez organomegalije. Noge bez edema.
U neurološkom nalazu: pacijent svestan, orijentisan, kranijalni nervi: nalaz bez ispada. Vrat slobodan, Meninglegalni znaci negativni. Na gornjim i donjim ekstremitetima: trofiko, tonus uredni. Gruba mišićna snaga: pronacija leve ruke. Obe noge: trofiko, tonus uredni. Gruba mišićna snaga: ispitano po grupama mišića uredno MTR pojačan. Plantarni odgovor je levo babinski. Proba peta koleno, umerena ataksija, a na gornjim ekstremitetima blaga ataksija. Hod ataksičan. Povremeno se registruju pokreti koji bi mogli odgovarati horeičnim. Dg: Sy Cervicalle. Ataxia. Hemiparesis lat. sin. Laboratorijske analize: krvna slika, hepatogram, renalni parametri, elektroliti, hemoglobina, srca normalne veličine. Bronhopneumonika infiltracija se ne vidi. MDCT glave: Stara ishemijska lezija u projekciji cerebeluma levo. Stara ishemijska lezija u projekciji moždanog stabla sa desne strane. Izraženi znaci cerebelarne atrofije. Superpentorijalno su ventrikularni sistemi i subarahnodalni prostori prošireni kao znak izraženih reduktivnih promena. Konsultacija sa psihijatrom, Prema CT nalazu, pacijent psihoorganski izmenjen. Objektivno: ispravno orijentisan, bez psihičkih distonija u sferi percepcija, urednog mišljenja. Pregled magnetnom rezonancijom, nalaz je ukazao na znake simetrične leukoencefalopatije/demijelinzacije u projekciji splenijuma korpusa kalozuma, periventrikularnoj beloj mazi, zadnjeg kraka kapsule interne, kortikospinalnog trakta, cerebelarno obostrano asocirane sa olivo-ponto-cerebelarnom atrofijom, diferencijalno dijagnostički u prvom redu u sklopu Adrenalnoleukodistrofije.

Zbog sumnje na adrenaloleukodistrofiju pacijent se prevodi na Kliniku za neurologiju radi daljeg ispitivanja. Elektromijelografi (EMG) nalaz: ukazuje na postojanje simetrične, umereno jake, senzorimotorne i aksonalno demijelinizirajuće polineuropatije. Doppler krvnih sudova vrata je bio uredan. Transkranijalni doppler: indeksi pulsatilnosti su globalno viši (izraženije u vertebrobazilarnom slivu), što ukazuje na povišen otpor u nivou malih krvnih sudova. Pregledom parenhima: nema patoloških heterogenosti u regijama SN, povećan je dijametar III komore, ostali nalazi uredni. Standardni EEG u trajanju od 20 minuta – uredan nalaz. Paraneoplastična antitela su bila uredna. U serumu je hitotriozidaza bila u granicama normale. Vrednosti masnih kiselina veoma dugih lanaca u serumu: C26: 0 = 0,27umg/ml (0,14–0,86); C26/C22 = 0,010 (0,014–0,086); C24/C22 = 0,49 (0,74–1,627). Neuropsihološko testiranje-primetne su smetnje u egzekutivnom funkcionalnom primarnom funkcionalanjum. Termin „egzekutivne funkcije” odnosi se na skup veština ili postupaka potrebnih za efikasno rešavanje problema, planiranje i organizovanje.
ADRENALOLEUKODISTROFIJA

**DISKUSIJA**

Adrenaloleukodistrofija (ALD) genetski je poremećaj koji prenosi majka na sina. Posledica je mutacija u genu ABCD1 smještenom na X hromozomu, što dovodi do nedostatka ili disfunkcije transmembranskog proteina ALDP (prenosi VLCFacyl-CoA estrazu iz citosola u peroksisom i time učestvuje u beta oksidaciji). Metabolički poremećaj se karakteriše narušenom beta oksidacijom masnih kiselina veoma dugih lanaca (C>22), pri čemu se one nagomilavaju u plazmi i tkivima. Akumulacija masnih kiselina veoma dugog lanca deluje toksično jer ima disruptivni efekt na strukturu, stabilnost i funkciju ćelijske membrane, smanjuje oslobađanje kortizola iz humanih adrenokortikalnih ćelija, destrušiše astrocite i oligodendrocite, uzrokuje oksidativni stres i oštećuje proteine, aktivira mikrogliju i apoptozu. Narušava sposobnost oligodendrocita i Švanovih ćelija da zadrže aksonalnu integritet, što rezultira oštećenjem aksona. Najčešće su oštećeni: mijelin u CNS-u, adrenalni korteks i Lajdigove ćelije u testisima. Kod ADL u vlaknu nervne ćelije nema mijelina, a bez mijelina nervne ćelije ne mogu normalno da funkcioniru (mijelinska opna deluje kao izolator i omogućava brzo provođenje električnih impulsa duž nervnih vlakana, kada je mijelin prekinut blokiran je prolaz jona i rastvora). Mijelin se ne može nadoknaditi pa se bolest s vremenom pogoršava. Dolazi do odumiranja funkcije organa i nemogućnosti kretanja (paralize). Incidenca ALD je 1: 17000 novorođenčadi. Moguće fenotipske prezentacije X-ALD kod osoba muškog pola: CEREBRALNA FORMA: dečija, adolescnetna, druga forma. ADRENOMIONEUROPATIJA (AML), SPINOCEREBELARNA FORMA (selektivno zahvatanje cerebelarne bele mase – veoma retko), SAMO ADISONOVA BOLEST, ASIMPTOMATSKI ili PRESINTOMATSKI pacijenti. Dečija cerebralna ALD najbrže progresivna, najteže kliničke slike, najčešće počinje u detinjstvu (nikada pre 2,5 godine) sa deficitom kognitivnih sposobnosti: kompromitovano vizuo-ali i vizuomotorno funkcionisanje ili pažnja i rezonovanje inicijalno: lošiji uspeh u školi, često se postavlja pogrešna dg ADHD. Dalje napredovanje bolesti dovodi da je bolesnik vezan za postelju, slep, u nemogućnosti da priča ili odgovara, hrani se preko nazogastrične sonde. Smrt obično nastupa 2 do 4 godine od početka simptoma. Rapidno neurološko pogoršanje je uzrokovano teškim inflamatornim procesom demijelinizacije koja primarno zahvata moždane hemisfere. Adolescentna i druga forma su red, simptomi slični kao kod dece, ali inicijalna progresija je sporija. Kod odraslih, retko je prepoznat početak kognitivne deterioracije od strane porodičnog ili radnog okruženja. Psihijatrijski poremećaji mogu imitirati
šizofreniju ili psihozu. Nekada: nagli početak i nakon perioda stabilnosti 10–15 godina. Trauma glave ili moždani udar mogu biti „okidači” za cerebralnu demijelinizaciju kod pacijenata sa X-ALD.

Skoro svi pacijenti sa X-ALD koji dožive odraslo doba razviju AML (adrenomioneropatija) u 30-im ili 40-im godinama života. Inicijalni simptomi su limitirani na kičmenu moždinu i periferne nerve. Pacijent razvija postepeno progresivnu spastičnu paraparezu, senzornu ataksiju sa narušenim vibrator-nim senzibilitetom, disfunkcijom sfinxtera, bolom u nogama i impotencijom. Polineuropatija koja se elektrofiziološki verifikuje kod većine pacijenata je aksonopatija. Pre pojave MRI, AML je često pogrešno dijagnostikovana kao multipla skleroza ili hereditarna spastična parapareza. Sporo progresivan fenotip prouzrokuje tešku motornu nesposobnost donjih ekstremiteta i manju ili nesignifikantnu slabost ruku.

Sporo progresivan fenotip prouzrokuje tešku motornu nesposobnost donjih ekstremiteta i manju ili nesignifikantnu slabost ruku. 70% AML pacijenata ima adrenokortikalnu i testikularnu insuficijenciju. Kosa im je tanka i počinje da se proređuje u ranom odraslim dobu.

U odsustvu biomarkera koji bi mogli da nagoveste evoluciju bolesti, MRI endokranijuma ostaje jedino oružje da se detektuje evolucija u ranom stadiumu. Biohemijska dijagnostika: skrining novorođenčadi kvantifikacijom C26:0 lizofosfatidilholina u kapi krvi – identifikuje presimptomatske pacijente sa X-ALD. Određivanjem koncentracije masnih kiselina veoma dugih lanaca – elevacija vrednosti u plazmi – potvrđuje se dijagnoza kod pacijenata sa Adisonovom bolešću. 15% žena sa X-ALD ima normalne nivoе VLCFA u plazmi, te je metoda dijagnostičkog izbora. Molekularna – analiza mutacije ABCD1 gena. Na ALD treba misliti kada su u pitanju: mlade muške osobe sa Adisonovom bolešću. Osobe sa kognitivnim ili neurološkim simptomima koji se pojačavaju, sa lezi-jama bele mase na MRI. Odrasli koji imaju fenotipsku prezentaciju hronične mijelopatije – povišene vrednosti VLCFA mogu da ukažu na druge poremećaje peroksizoma.

Važno je praćenje pacijenata zbog rane detekcije: adrenokortikalne insuficijencije i cerebralne ALD da bi se sprovela terapija. Uprkos značajnom stepenu rizika od mortaliteta, alogena transplantacija kostne srži ostaje jedina terapijska intervencija koja može da zaustavi progresiju cerebralne demijelinizacije kod bolesnika sa X-ALD-om, ako se procedura dovoljno rano sproveđe.

Dečacima, ili odraslima, obolelima koji nemaju Adisonovu bolest, potrebna je jedanput godišnje kontrola kod endokrinologa. Dečaci bez neurološkog deficita: pratiti radiološke znake cerebralne ALD: MRI mozga svakih 6 meseci kod dece uzrasta 3 do 12 godina. Posle 12. godine incidencenę dečije cerebralne forme opada, ali MRI treba raditi jedanput godišnje. Zbog mogućnosti rapidne
progresije bolesti, savetuje se da, čim se primete MRI abnormalnosti, treba raditi transplantaciju kostne srži.

Lorencovo ulje nije pokazalo da zaustavlja progresiju bolesti, čak i ako normalizuje nivo masnih kiselina u plazmi, ali kod presimptomatskih dečaka odlaže početak neuroloških simptoma.

**ZAKLJUČAK**

Pacijentu A. A. je u detinjstvu dijagnostikovan primarni hipokorticizam, tada se smatralo da je hipokorticizam nastao kao posledica tuberkoloznog procesa. Pacijent od 45. godine života ima neurološke tegobe koje je zanemarivao. U vreme hospitalizacije na našoj klinici, neurološke tegobe značajno narušavaju kvalitet života. Stanje spinocerebelarne ataksije i diskretnog levostranog piramidalnog deficita sa inkontinencijom urina i psihijatrijskim problemima zahtevao je dodatno ispitivanje. Pacijentu je u saradnji sa Klinikom za neurologiju sprovedena dijagnostika. Rezultati ispitivanja su pokazali da pacijent boluje od X-zavisne adrenaloleukodistrofije sa zahvaćenostiću centralnog i perifernog nervnog sistema. Hipokorticizam dijagnostikovan u ranoj životnoj dobi je bio prvi znak bolesti i rana manifestacija X-vezane adrenaloleukodistrofije.
Abstract: Introduction: Adrenoleukodystrophy (ALD) is a disease characterized by the accumulation of very long chain fatty acids in tissues throughout the body. The most severely affected tissues are the myelin in the central nervous system, the adrenal cortex and the Leydig cells in the testes. Clinically, ALD is a heterogeneous disorder, presenting with several distinct phenotypes, and no clear pattern of genotype-phenotype correlation.

Case report: Patients S.A. 50 years old, in the third year of life was diagnosed with primary adrenal insufficiency. From the age of 45 he feels, headache, dizziness, bends to the right when walking, night incontinence of urine. Talking to himself, the last year goes to the cemetery every day, occasionally crying without control and remembrance. Condition with spinocerebellar ataxia and a left pyramidal defect with incontinence of urine and psychiatric problems required re-examination. In consultation with neurologist at the Department of Neurology, investigations have shown that patient is suffering from X-linked adrenoleukodystrophy with affected central and peripheral nervous system.

Adrenoleukodystrophy (ALD) is caused by mutations in ABCD1, a gene located on the X chromosome that codes for ALD, a peroxisomal membrane transporter protein. The exact mechanism of the pathogenesis of the various forms of ALD is not known. it is a disorder of peroxisomal fatty acid beta oxidation which results in the accumulation of very long chain fatty acids in tissues throughout the body. The most severely affected tissues are the myelin in the central nervous system, the adrenal cortex and the Leydig cells in the testes. Clinically, ALD is a heterogeneous disorder, presenting with several distinct phenotypes, and no clear pattern of genotype-phenotype correlation. As an X-linked disorder, ALD presents most commonly in males, however approximately 50% of heterozygote females show some symptoms later in life.
ADRENOLWKODYSTROPHY

tely two-thirds of ALD patients will present with the childhood cerebral form of the disease, which is the most severe form. It is characterized by normal development in early childhood, followed by rapid degeneration to a vegetative state. The other forms of ALD vary in terms of onset and clinical severity, ranging from adrenal insufficiency to progressive paraparesis in early adulthood (this form of the disease is typically known as adrenomyeloneuropathy).

Conclusion: In our case hypocorticism was the first sign of X-linked adrenoleukodystrophy.

In male patients with hypocorticism X-linked adrenoleukodystrophy should always be excluded as one of the possible causes of primary adrenal insufficiency.

Key words: adrenaloleukodystrophy, Morbus Addison, X-linked recessive genetic disorder.

INTRODUCTION

Adrenoleukodystrophy is an X-linked recessive genetic disorder caused by an abnormality in the ABCD1 gene on the X chromosome. This condition affects the white matter of the nervous system and the adrenal cortex. Some affected individuals have adrenal insufficiency, which means that reduced amounts of certain hormones such as adrenaline and cortisol are produced, leading to abnormalities in blood pressure, heart rate, sexual development and reproduction. Some of those affected experience serious neurological problems that can affect mental function and lead to disability and reduced life span. This condition has been categorized into six types based on symptoms and age of onset: childhood cerebral ALD, adolescent cerebral ALD, adrenomyeloneuropathy, adult cerebral ALD, adrenal insufficiency only and ALD that occurs in females.

ALD is the most common leukodystrophy, accounting for about half of all leukodystrophies. The prevalence is approximately 1/20,000-1/50,000 births and most of those affected are boys. Approximately half of all females who carry the abnormal ABCD1 gene will develop some symptoms of ALD. The condition occurs in all ethnic groups.

Addison disease is a rare disorder of the adrenal glands. In the majority of cases the cause is not known. Symptoms may result from chronic and progressive low level function (hypofunction) of the outer layers (cortex) of the adrenal gland resulting in deficiencies of the hormones cortisol and aldosterone. The deficiency of these hormones leads to low levels of sodium and chloride and high levels of potassium (electrolyte imbalance) in the blood. The imbalance of electrolytes causes increased water excretion, low blood pressure (hypotension), and abnormally low levels of water in
the body (dehydration). The major symptoms of Addison disease may include fatigue, weakness, loss of appetite (anorexia), frequent urination, gastrointestinal discomfort and changes in skin pigmentation.

The concentration of very long fatty acids (VLFA) in blood plasma is elevated in 99% of males with ALD and in approximately 85% of female carriers of the abnormal ABCD1 gene. Molecular testing for the ABCD1 gene is available and is used primarily to confirm a diagnosis if other testing is not conclusive, to provide genetic counseling to family members and for prenatal diagnosis. Adrenal function tests are abnormal in 90% of boys with ALD who have neurologic symptoms and in approximately 70% of men with adrenomyeloneuropathy.

Treatment: The abnormal adrenal function is treated with corticosteroid replacement therapy. Bone marrow transplantation has been successful in individuals who are in the early stages of ALD. Affected individuals can benefit from supportive care from psychologists, educators, physical therapists, urologists, and family and vocational counselors. Genetic counseling is recommended for affected individuals and their family members.

**CASE REPORT**

Patient A A, 50 years old, was hospitalized due to fatigue, headaches, dizziness, drifting to the right when walking, bedwetting, occasional urinary incontinence. The heteroanamnesis revealed other symptoms such as talking to himself, spending time at the cemetery every day for the past year, occasional uncontrollable yelling without being able to remember it afterwards. At the age of 3, the patient suffered from lung TB, and was diagnosed with Addison’s disease quickly thereafter at the Institute for Mother and Child, where we was monitored until the age of 16. He had been receiving a hydrocortisone replacement therapy of 10+10+50 mg. In 1991 (at the age of 28) he had stopped the replacement therapy on his own and was without therapy for 10 years. During this time he had been feeling well even during periods of flu with fever (no fatigue, skin did not become darker then before). Therapy was reintroduced in December 2002 when he visited a doctor because of headaches. His skin is darker then it was in his childhood. Diffuse hair loss since the age of 20. Occipital neuralgia since 2004, which had spontaneously stopped in the meantime. During the same period he had started to drift mostly to the right when walking, especially upon sudden standing but also without sudden body movements. Personal history: tonsillectomy in childhood, lung TB at the age of 3. Family history: mother was treated at the Clinic of Neurology in 1992 (at the age of 64) for tingling in her legs, difficulty walking and unsteady gait; diagnosis: hereditary spastic paraparesis. His aunt, mother’s sister, had walking problems that started around the age of 40, no details of disease are available. He is married and has two sons.
ADRENOLEUKODYSTROPHY

Patient has a normal osteo-muscular structure, BMI 19.3 kg/cm², afebrile, eu-pnoeic, acyanotic, anicteric, diffuse slightly darker skin, normal buccal mucosa color, discretely darker gingiva, darker pigmented palmar furrows. Duly hydrated without peripheral lymphadenopathy and signs of hemorrhagic syndrome. Actively mobile, ataxic gait. Diffuse hair thinning, lung function test results normal. Heart rhythm normal, sounds clear, no murmurs. TA 110/75 mmHg, pulse 61/min. Abdomen at the chest level palpatory insensitive to pain, without organomegalia. No oedema in legs.

Neurological examination results: patient is conscious, oriented. Cranial nerves: results normal. Neck free, meningeal signs negative. Upper and lower extremities: muscle mass, tonus are normal. Gross muscular strenght: pronation of left arm. Slight sinking of both legs, gross muscular strenght: tested by groups of muscles, normal result, MTR enhanced. Plantar response: Babinski response on the left. Heel-knee test: moderate ataxia; upper extremities: mild ataxia. Ataxic gait. Occasionally, movements have been registered that correspond to choreic. Diagnosis: Sy Cervicalle. Ataxia. Hemiparesis lat. sin. Laboratory tests: blood count, hepatogram, renal parameters, electrolyte status: normal result; inflammatory syndrome: negative. Urine result normal. Hormonal status of the thyroid gland within normal limits. ACTH high (1800), hydrocortisone day curve indicates adequate supstitution. Low aldosterone, PRA normal. Testosterone within normal range. Tumor markers within normal range. EKG sinus rhythm, SF 65/min, PR 0.16 sec, incomplete right bundle branch block, no pathological changes in ST segment and T wave. Lungs and heart RTG: accentuated bilaterally hilar and basal lung markings. Normal heart shadow. Bronchopneumonic infiltration not visible. MCDT head scan: old ischemic lesions in the cerebellar projection on the left side. Old ischemic lesions in the brain stem projections on the right side. Pronounced signs of cerebellar atrophy. Supratentorial ventricular systems and subarachnoid spaces are dilated as a sign of reductive changes. Consultation with a psychiatrist. According to CT result patient has undergone psycho-organic changes. Objectively: properly oriented, without mental dystonia in the sphere of perception, orderly thinking. Cranial MRA: result indicates signs of symmetrical leukoencephalopathy / demyelination in the projection of splenium of the corpus callosum, periventricular white matter bicipial-occipital, posterior limb of internal capsule, corticospinal tract, bilateral cerebellar association with olivopontocerebellar atrophy, in terms of differential diagnosis primarily within adrenoleukodystrophy.

Due to the suspected adrenoleukodystrophy the patient is transferred to the Clinic of Neurology for further testing. Electromyelography (EMG) result: indicates the existence of symmetrical, moderately severe sensorimotor and axonal demyelinating polyneuropathy. Doppler ultrasound exam of blood vessels in the neck was normal. Transcranial doppler: pulsatility index is generally higher (more pronounced in vertebrobasilar basin), indicating an increased resistance at the small blood vessels level. Examination of parenchyma: no pathological heterogeneity in SN regions, increased
diameter of chamber III, other results normal. Standard 20 minute EEG - normal findings. Paraneoplastic antibodies were normal. Serum levels of chitotriosidase were normal. Very long chain fatty acids serum levels: C26: 0 =0,27ug/ml (0,14-0,86); C26/C22 = 0,010 (0,014-0,086); C24/C22 = 0,49 (0,74-1,627). Neuropsychological assessment: disturbances of executive functions are noticable. The term executive functions refers to a set of skills or processes that are necessary for effective problem solving, planning and organizing, self controle, initiative, troubleshooting and cognitive control of behavior. Almost all executive functions theories are a result of desire to understand the role of the frontal lobe in cognition.

**DISCUSSION**

Adrenoleukodystrophy (ADL) is a genetic disease that is passed on by mother to son. It results in the mutation in ABCD1, a gene located on the X chromosome, leading to a deficiency or dysfunction of the transmembrane protein ALDP (transports VLCFacyl-CoA esterase from the cytosol to peroxisome, thereby participating in the beta-oxidation). Metabolic disorder is characterized by disturbed beta oxidation of the very long chain fatty acids (C>22), wherein they are accumulated in the plasma and tissues. The accumulation of very long chain fatty acids is highly toxic since it has a disruptive effect on the structure, stability and function of the cell membrane, reduces the release of cortisol from human adrenocortical cells, destroys astrocytes and oligodendrocytes, causes oxidative stress and damage to proteins, activates microglia and apoptosis. It impairs the ability of oligodendrocytes and Schwann cells to maintain axonal integrity, resulting in damage to the axons. Mostly damaged are: the myelin in the CNS, the adrenal cortex and the Leydig cells in the testes. In case of ALD there is no myelin in the nerve cell fiber, and without myelin the nerve cells cannot function properly (myelin membrane acts as an insulator and enables fast conduction of electric impulses along nerve fibers; when myelin is interrupted, the passage of ions and solvents is blocked). Since myelin cannot be recovered, the disease worsens with time. It results in organ failure and inability to move (paralysis). The incidence of ALD is 1: 17000 of newborns. Possible phenotypic presentation of X-ALD in males: CEREBRAL FORM: child, adolescent, adult form.

**ADRENOMYONEUROPATHY (AML), SPINOCEREBELLAR FORM (selective inclusion of the celebellar white matter - very rare), ONLY ADDISON’S DISEASE, ASYMPTOMATIC or PRESYMPTOMATIC patients. Childhood cerebral ALD is most progresive, with the most severe clinical picture, usually begins in childhood (never before the age of 2.5) with a deficit of cognitive abilities: compromised visuospatial and visuomotor functioning or attention and reasoning, initially; poor performance in school, often misdiagnosed as ADHD. Further progression of the disease results in patient being bedridden, blind, unable to talk or respond, is fed
ADRENOLEUKODYSTROPHY

though a nasogastric tube. Death usually occurs 2 to 4 years after the onset of symptoms. Rapid neurological deterioration is caused by the severe inflammatory process of demyelination that primarily affects the cerebral hemispheres.

Adolescent and adult forms are less frequent, symptoms are similar to those of children, however the initial progression is slower. In adults, the beginning of cognitive deterioration is rarely recognized by family or work environment. Psychiatric disorders may mimic schizophrenia or psychosis. Sometimes: sudden onset after a period of stability of 10-15 years. Head trauma or stroke may also “trigger” cerebral demyelination in patients with X-ALD.

Almost all patients with X-ALD who live to adulthood develop AML (adrenomyoneuropathy) in their 30s or 40s. Initial symptoms are limited to spinal cord and peripheral nerves. The patient gradually develops progressive spastic paraparesis, sensory ataxia with impaired vibratory sensibility, sphincter dysfunction, pain in legs and impotence. Polyneuropathy confirmed by electrophysiological tests in most patients is axonopathy. Prior to the use of MRI, AML was often misdiagnosed as multiple sclerosis or hereditary spastic paraparesis. The slowly progressive phenotype causes severe motor impairment of lower extremities and minor or insignificant weakness of arms. 70% of the AML patients have adrenocortical and testicular insufficiency. Their hair is thin and the hair loss begins in early adulthood.

In the absence of biomarkers that could imply the evolution of the disease, the endocranial MRI remains the only means of detecting the evolution in the early stages. Biochemical diagnostics: screening of newborns by quantification of C26:0 lysophosphatidylcholine in a drop of blood identifies the presymptomatic patients with X-ALD. Determining the very long chain fatty acids levels - elevated plasma levels is a confirmation of diagnosis in patients with Addison’s disease. 15% of women with X-ALD have normal VLCFA plasma levels, so that the diagnostic method of choice is the molecular analysis of the ABCD1 gene mutation. ALD needs to be considered in young male patients with Addison’s disease. People with cognitive or neurological symptoms which are amplified, with white matter lesions on MRI. Adults who have chronic myelopathy phenotype presentation - increased levels of VLCFA may indicate other peroxisome disorders.

It is important to monitor patients for early detection of adrenocortical insufficiencies and cerebral ALD in order to implement therapy. Despite a significant mortality risk level, allogeneic bone marrow transplantation remains the only therapeutic intervention that can stop the progression of cerebral demyelination in patients with X-ALD, if the procedure is performed early enough.

Boys or adult patients not diagnosed with Addison’s disease require an annual examination by an endocrinologist. Boys without neurological deficit: monitor the radiological signs of cerebral ALD: brain MRI every 6 months in children aged 3 to 12. After the age of 12 the incidence of cerebral form drops, but the MRI should be
performed once a year. Due to the possibility of rapid progression of the disease, it is advisable to perform bone marrow transplant as soon as abnormalities appear on the MRI.

Lorenzo’s Oil has not proven to stop the progression of the disease, even if it regulates the plasma fatty acids levels, however in presymptomatic boys it delays the onset of neurological symptoms.

**CONCLUSION**

Patient A. A. was diagnosed with primary hypocorticism in childhood; it was then believed that the hypocorticism was the result of the tuberculosis. Since the age of 45, the patient has had neurological symptoms which he has been neglected. At the time of hospitalization at our clinic, neurological symptoms have significantly impaired his quality of life. The spinocerebellar ataxia and the discreet left side pyramidal deficit with urine incontinence and psychiatric problems required additional testing. Diagnostics have been performed for the patient in cooperation with the Clinic of Neurology. Test results have shown that the patient suffers from X-linked adrenoleukodystrophy with affected central and peripheral nervous system. Hypocorticism that was diagnosed at an early age was the first sign of the disease and early manifestation of the X-linked adrenoleukodystrophy.

**REFERENCE**

1. Steinberg, S. J.; Moser, A. B.; Raymond, G. V.; Pagon, R. A.; Bird, T. D.; Dolan, C. R.; Stephens, K.; Adam, M. P. (1993). “X-Linked Adrenoleukodystrophy”. PMID 20301491.
2. - Adrenoleukodystrophy”. Johns Hopkins University. Retrieved 2012-06-27.
3. Sandlers, Y.; Moser, A. B.; Hubbard, W. C.; Kratz, L. E.; Jones, R. O.; Raymond, G. V. (2012). “Combined extraction of acyl carnitines and 26:0 lysophosphatidylcholine from dried blood spots: Prospective newborn screening for X-linked adrenoleukodystrophy”. Molecular Genetics and Metabolism 105 (3): 416–420.
4. Hubbard, W. C.; Moser, A. B.; Liu, A. C.; Jones, R. O.; Steinberg, S. J.; Lorey, F.; Panny, S. R.; Vogt Jr, R. F.; MacAya, D.; Turgeon, C. T.; Tortorelli, S.; Raymond, G. V. (2009). “Newborn screening for X-linked adrenoleukodystrophy (X-ALD): Validation of a combined liquid chromatography–tandem mass spectrometric (LC–MS/MS) method”. Molecular Genetics and Metabolism 97 (3): 212–220.
5. Raymond, G. V.; Jones, R. O.; Moser, A. B. (2007). “Newborn screening for adrenoleukodystrophy: Implications for therapy”. Molecular diagnosis & therapy 11 (6): 381–384.
6. Cartier, N.; Aubourg, P. (2009). “Hematopoietic Stem Cell Transplantation and Hematopoietic Stem Cell Gene Therapy in X-Linked Adrenoleukodystrophy”. Brain Pathology 20 (4): 857–862.
7. Petryk, A.; Polgreen, L. E.; Chahla, S.; Miller, W.; Orchard, P. J. (2012). “No evidence for the reversal of adrenal failure after hematopoietic cell transplantation in X-linked adrenoleukodystrophy”. Bone Marrow Transplantation 47 (10): 1377–8.

8. Engelen, M. (2012). “Peroxisomal Leukoencephalopathy”. Seminars in Neurology 32 (1): 42–50.