Tatjana Nišić, Jasmina Ćirić, N. Dragašević-Mišković[1], M. Stojanović, Biljana Beleslin, Mirjana Stojković , Slavica Savić, Tijana Lalić, M. Barać, Miloš Žarković

ADRENOLEUKODYSTROPHY

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. Approxima-

[1] Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia; Clinic of Neurology, Clinical Center of Serbia, nisictanja@gmail.com

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.

Patient has a normal osteo-muscular structure, BMI 19.3 kg/cm^2, afebrile, eupnoeic, acyanotic, anicteric, duffuse slightly darker skin, normal buccal mucosa color, discretely darker gingiva, darker pigmented palmar furrows. Duly hydrated without peripheral lymphadenopathy and signs of hemorragic sydrome. 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 organomegaly. 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 venticular 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 leukoencephalopaty / demyelination in the projection of splenium of the corpus callosum, periventricular white matter biparietal-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

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 shizophrenia 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 endocranium 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 adrenocortial insufficiences 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.

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