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Case Report / Приказ случаја

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Морфолошки и биохемијски показатељи ретке наследне адренолеукодистрофије везане за *X*-хромозом код детета

SUMMARY

Introduction Adrenoleukodystrophy (ALD) is a rare genetic disease, caused by mutations in *ABCD1* gene located on X chromosome (X-ALD). This condition is underdiagnosed worldwide.

Case Outline We present a clinical case of a six-year-old boy with childhood cerebral X-ALD. MRI of the patient's brain showed bilateral lesions similar to adrenoleukodystrophy in parietal-occipital lobes of the brain. Plasma very long chain fatty acids (VLCFA) determination test was performed to confirm X-ALD. An elevated level of C26 and C26/C22 ratio observed in the VLCFA test confirmed the diagnosis of X-ALD.

Conclusion An effective treatment of X-ALD can be established for early-stage cerebral ALD. Early diagnosis of X-ALD is possible with presented patterns (MRI and biohemical analysis).

Keywords: X-linked adrenoleukodystrophy; fatty acids; MRI

САЖЕТАК

Увод. Адренолеукодистрофија (АЛД) је ретка наследна болест услед мутације *ABCD1* гена на *X* хромозому (*X*-АЛД) која се ретко дијагностикује.

Приказ болесника Приказан је случај шестогодишњег дечака са церебралном *X*-АЛД. МР мозга је показао обостране лезије сличне АЛД у перијето-окципиталном режњу. Тест веома дугих ланаца масних киселина у плазми је показао повишен ниво *C*26 и однос *C*26/*C*22 и потврдио дијагнозу *X*-АЛД.

Закључак Ефикасно лечење *X*-АЛД је могуће у раној фази болести када се дијагноза може поставити наведеним морфолошким и биохемијским показатељима.

Кључне речи: *X*-везана адренолеукодистрофија, масне киселине, МР

INTRODUCTION

Adrenoleukodystrophy is a rare genetic disease caused by mutations in *ABCD1* gene which maps to Xq28 chromosome, thus it is commonly called X-linked adrenoleukodystrophy (X-ALD). The occurrence of X-ALD is 1 in 20 000 of 50 000 individuals worldwide [1, 2]. *ABCD1* gene mutation causes the encoded ATP-binding cassette transporter protein inability to transfer CoA-activated very long chain fatty acids (VLCFA) into peroxisomes for their β-oxidation. Non-degraded VLCFA (carbon atoms ≥C22) accumulate in tissues or body fluids and usually cause nervous system demyelination and adrenal insufficiency [2, 3]. Several phenotypes of X-ALD can be distinguished: childhood cerebral ALD, adolescent cerebral ALD, adult cerebral ALD, adrenomyeloneuropathy, Addison disease only and women with X-ALD [2].

The aim of this study is report of a rare genetic disease caused by mutations in *ABCD1* gene located on X chromosome (X-ALD).

CASE REPORT

We present a case of childhood cerebral X-ALD in a six-year-old boy. The onset of the disease was observed at the age of 5 years. The first sign of the disease was an episodic lateral deviation of the right eye. Vomiting and febrile temperature appeared approximately at the same time. Symptomatic treatment was administered. Complaints of reduced hearing and eyesight appeared three months later. Furthermore, chronic bilateral neuritis of cochlear nerves was diagnosed by

otorhinolaryngologist and was treated with Piracetam and vitamins B6, B12. Piracetam (900 milligrams per day) was prescribed to prevent vertigo and vitamins B6, B12 were prescribed to treat neuritis. Blurred vision was corrected with glasses. There was no response to the treatment and the condition was slowly aggravating. The boy became hulky, complained of headaches in the forehead followed by sleep and articulation disorders . The patient was hospitalised in pediatric neurology unit because of complaint of blindness, nine months after the first symptom of the disease was recorded. On clinical examination the child's sight was diagnosed as abnormal, he could not appropriately respond to to the given orders or questions. Tendon reflexes and the Babinski sign were stronger on the left half of the lower limbs. Photoreaction on the left pupil was reduced while there was no reaction observed on the right . Meningeal symptoms were negative. Other systems did not show any abnormalities. Blood count and chemistry, electrolytes, glucose levels were normal. Computer tomography (CT) with and without contrast was performed. There was a bilateral lesion similar to adrenoleukodystrophy in parietal-occipital lobes of the brain. After that, brain magnetic resonance imaging (MRI) and level of adrenocorticotropic hormone (ACTH) were performed. MRI showed bilateral symmetrical areas of hyperintense T2 weighted signals noted in temporal, occipital and parietal white matter of cerebrum. Post-contrast study showed peripheral enhancement of these areas. Similar hyperintense areas were seen in pons and mesencephalon corresponding to medial and lateral lemniscus (Figure 1). These classical symmetrical occipital white matter lesions were typical of ALD [4]. ACTH was highly increased, so replacement therapy with hydrocortisone was recommended.

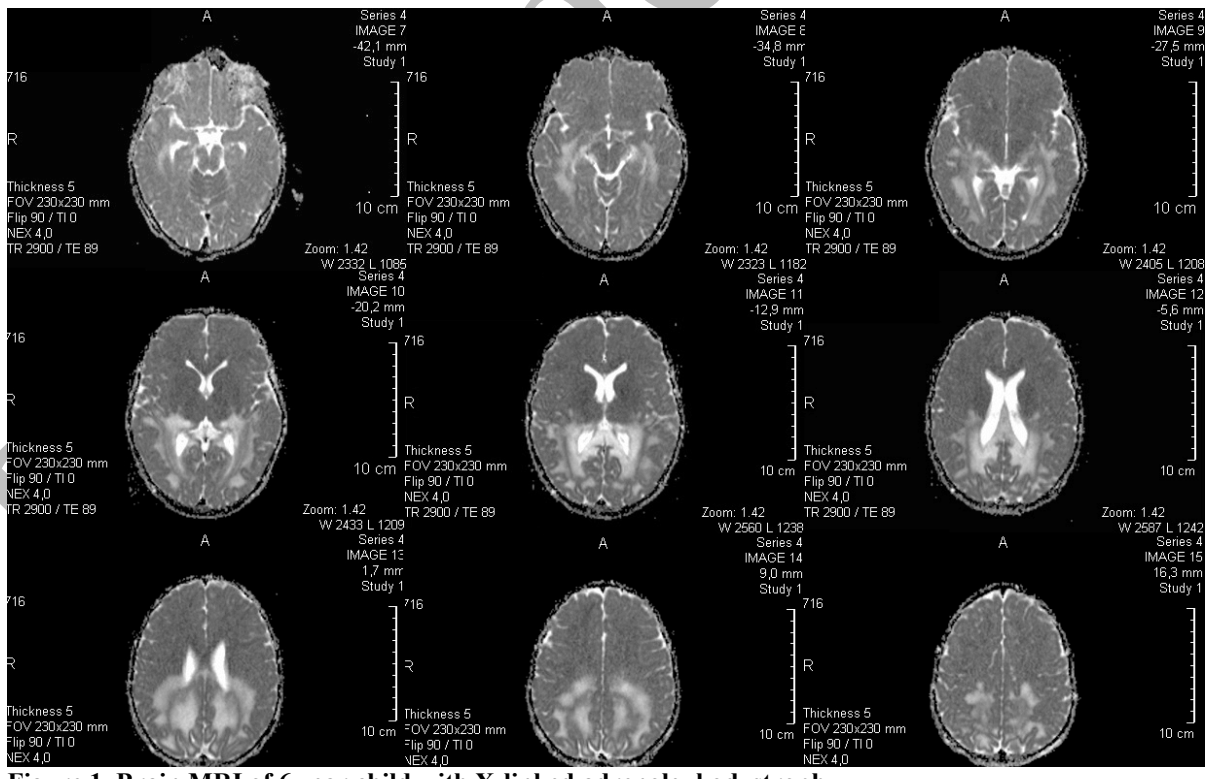

Figure 1. Brain MRI of 6 year child with X-linked adrenoleukodystrophy.
Bilateral symmetrical areas of hyperintense T2 weighted signals noted in temporal, occipital and parietal white matter of cerebrum. Post-contrast study showed peripheral enhancement of these areas. Similar hyperintense areas were in pons and mesencephalon corresponding to medial and lateral lemniscus.

Other instrumental examination involved BERA (brainstem evoked response audiometry) and abdominal ultrasound which were normal.

Plasma very long chain fatty acids determination test confirmed the diagnosis of X-ALD. There was an elevated level of C26 and C26/C22 ratio in the VLCFA test (Table 1).The diagnosis was made according to the clinical presentation, MRI, and the fatty acid profile, however *ABCDI1* gene mutations on the X chromosome were not tested.

Table 1. X-ALD patient's and 2 years old healthy brother's profile of very long chain fatty acids.

Long chain fatty acid	X-ALD patient	Healthy brother	Normal range
C22	41.3 µmol/l	36.3 µmol/l	41.9–119 µmol/l
C24	77.8 µmol/l	29.4 µmol/l	20.3–96.1 µmol/l
C26	**3.34 µmol/l**	0.36 µmol/l	0.18–1.06 µmol/l
C24/C22	**1.883**	0.812	0.39–1.38
C26/C22	**0.08**	0.01	0.002–0.021

C – Carbon atoms number of fatty acids chain; C24/C22 – ratio; C26/C22 – ratio.

Apart from the proband, his healthy 2-year -old brother was also tested for the fatty acids profile. It was not elevated, even C22 was below the range (Table 2), thus the possibility of the onset of the disease in the younger sibling was excluded.

DISCUSSION

X-linked ALD leads to demyelination of the nervous system, adrenal insufficiency and accumulation of long-chain fatty acids [2]. The clinical course in ALD is characterised by behavioural disorders, ataxia, visual loss, decreased hearing and epileptic seizures, followed by mental deterioration, psychosis and death. Abnormal skin pigmentation and other features of adrenal insufficiency may become apparent before neurological symptoms. The diagnosis of X-ALD is confirmed by analysing the plasma levels of VLCFAs or identifying aberrant mutations in the *ABCD1* gene [1].

X-linked ALD is a white matter disease, which can initially present with psychiatric symptoms and thus be misdiagnosed as a primary psychiatric disorder. Behavioural and emotional changes develop prior to progressive deterioration of vision, hearing and motor functions. In our patient, the first symptoms were observed as episodic lateral deviation of the right eye. Within a few months, the child's cognitive abilities and speech deteriorated and difficulty in walking developed accompanied with behaviour changes.

Many tests had been performed over approximately eleven months until the diagnosis of X-linked ALD was confirmed by VLCFA analysis. The main goal of this clinical case is to draw attention of doctors to recognize X-ALD as early as possible, because the only possible treatment is for the early-stagedisease . It is the allogeneic haematopoietic cell transplantation (HCT) that allows to stabilize the disease [5].

The important point is that the patient has a 2 year old brother whose fatty acids profile showed no abnormalities. Thus, the conclusion was that he would not develop a neurologic disease later on. Prior risk for the brother in current X – linked disorder to inherit the mutation was increased, , since

the mother is a possible carrier of the mutation. However, a de novo mutation cannot be excluded in the affected child, as well as gonadal mosaicism in the mother. Early diagnosis (presymptomatic), could be useful due to some new therapeutic methods, currently available.

Previously the treatment of X-ALD was symptomatic: for example, steroid use for adrenal insufficiency and psychotropics for psychiatric symptoms. No clearly effective treatments are available, although Lorenzo's oil (4:1 glyceryl trioleate and glycerytrierucate) used before the age of 6 may reduce the probability of developing neurological deficits in later life [4, 5]. A new mode of treatment for X-ALD is focused on haematopoietic cell transplantation especially in the early-stage ALD. Good therapeutical outcomes are achieved only if the treatment is taken at an early stage of the disease. In addition, if the phase of demyelination has started, HSC transplantation leads to the worsening of the disease. Also, the transplantation does not improve adrenal function. This shows the importance of the benefits of an early diagnosis. Also, *ABCD2*, which encodes ALDRP or ABCD2 proteins and which is the closest homolog of *ABCD1* could be potentially used in gene therapy. Induced overexpression of *ABCD2* gene could be a possible treatment for X-ALD [6]. Recombinant adeno-associated virus serotype 9 (rAAV9) vectors were used for the delivery of the human *ABCD1* gene to the mouse central nervous system (CNS) [7, 8]. Current article points to the importance of confirmation of the diagnosis by radiological and biochemical methods, which is beneficial for genetic prognosis, early treatment and sibling testing.

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