X-linked Adrenoleukodystrophy Initially Presenting with Severe Deafness

**ABSTRACT** X-linked adrenoleukodystrophy is the most common peroxisomal disorder characterized by progressive demyelination of the central nervous system, and adrenal insufficiency. A thirteen-years-old male presented with hearing loss and night crying. He was talking loudly because of the deafness, and his skin was hyperpigmented. Adrenocorticotropic hormone (ACTH) level was increased and cortisol level was low in hormonal evaluation. Very long chain fatty acids were studied for suspected adrenoleukodystrophy, and elevated plasma C26 level led to the diagnosis. Molecular genetic analysis revealed hemizygous deletion of exons 6 to 9 in ABCD1 gene. Although poor school performance, attention deficit, behavioral changes, quadriplegia, cerebral ataxia, visual and hearing impairment, adrenal insufficiency are classical clinical findings of adrenoleukodystrophy, rarely severe deafness can be the initial symptom.

**Keywords:** Adrenoleukodystrophy; ABCD1 protein, human; hearing loss, central

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**CASE REPORT**

A thirteen-year-old male presented with the complaints of hearing loss and night crying. He was healthy until 2 weeks before clinical findings. He was born after an uneventful pregnancy by spontaneous vaginal delivery. The
patient was the third child of a non-consanguineous Turkish couple. They also had two healthy sons and a daughter. Prenatal, obstetric and family history was unremarkable, and the patient’s school performance was normal.

His body weight was 41.7 kg (10-25% percentile), height was 167 cm (90-97% percentile). His skin was hyperpigmented and he was talking loudly because of the deafness.

Bilateral severe sensorineural hearing loss was identified in audiometry and tympanogram. Basic metabolic studies were studied due to the deafness and night cries. Blood lactate, pyruvate, biotinidase activity, homocysteine, plasma amino acid and blood acylcarnitine analysis, urine organic acid and urine amino acid analysis were normal. Complete blood count, blood glucose, and electrolytes were within normal limits. ACTH level was increased and cortisol level was low in hormonal evaluation. Very long chain fatty acids were studied for suspected ALD, and elevated plasma C26 level led to the diagnosis (Table 1).

Deafness and night cries were associated with an intracranial event. Cranial MRI revealed bilateral abnormal hyperintense lesions in central pons, corticobulbar and corticospinal tracts, demyelination of auditory and visual tract involving the region of parietooccipital and posterior temporal white matter compatible with ALD (Figure 1).

Right dominant, isolated spikes and sharp wave activity were seen in frontosantral temporal region in Electroencephalography (EEG) and sodium valproate was started for prophylaxis.

The diagnosis is established by detection of a hemizygous deletion of the exons between 6 to 9 in ABCD1 gene in agarose gel electrophoresis and confirmed with Multiplex ligation dependent probe amplification (MLPA).

Sodium valproate, aripiprazole, hydrocortisone, Lorenzo’s oil and diet were started for treatment and bone marrow transplantation was applied to him four weeks after the diagnosis. This case report was written after receiving informed consent from the family.

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<th>TABLE 1: Laboratory findings of the patient.</th>
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Abbreviations: Hb, Hemoglobin; WBC, White blood cell; PLT, platelet; ACTH, Adrenocorticotrophic hormone. ACTH level (N<46), cortisol level (N:6.7-22.6), C26 level (N:0-0.92).

FIGURE 1: The patient’s cranial MRI findings. Axial T2-weighted images reveal abnormal hyperintense lesions including bilateral central pons, anterior bulbus, anterior cerebral peduncles, and corticospinal tracts (a, b). Auditory tract and visual tract demyelination involving the region of parietooccipital and posterior temporal white matter (b-d). Sagittal T2W image shows abnormal hyperintense lesion in splenium of the corpus callosum (e). Post contrast T1W images show contrast enhancement of the parietooccipital region (f-h).
**DISCUSSION**

ALD is a progressive neurodegenerative disease caused by mutations in \textit{ABCD1} gene and characterized by VLCFA accumulation in brain and other tissues. Childhood cerebral form, adrenomyeloneuropathy, isolated Addison’s disease, asymptomatic form, adolescent cerebral form and adult cerebral form are various forms of ALD. Poor school performance, attention deficit, behavioral changes, severe visual and hearing impairment can be seen in affected patients.\textsuperscript{4,5} Our case is adolescent cerebral form of ALD. He was healthy until 2 weeks prior to the referral.

Hearing loss is relatively common in children, and occurs in approximately two out of every 1,000 births. 50% of reported diagnoses had a primary genetic defect.\textsuperscript{6} Late onset Zellweger spectrum disorder (\textit{PEX6} gene mutation), Canavan Disease (\textit{ASPA} gene), Heimler Syndrome (\textit{PEX1} and \textit{PEX6} mutations), Waardenburg syndrome Type-2 (\textit{MITF} gene) and 4 (\textit{EDNRB} gene) should be considered in the differential diagnosis of skin hyperpigmentation and deafness.\textsuperscript{7,8}

Mehta et al. reported 612 non syndromic (92.7%) and 48 (7.3%) syndromic patients with sensorineural hearing loss.\textsuperscript{6} Usher and Waardenburg syndromes have been identified as the most common causes of hearing loss for syndromic origin. \textit{GJB2} mutations were found to be the most common causes of nonsyndromic origin.

Hyperhomocysteinemia, high levels of factor VIII, other acquired and inherited thrombophilic risk factors described in patients with sudden sensorineural hearing loss.\textsuperscript{9} Homocysteine and lipid levels of our patient were normal.

Some of the metabolic diseases that can cause hearing loss are biotinidase deficiency, mitochondrial disorders and lysosomal storage diseases.\textsuperscript{10,11} Biotinidase activity and other basic metabolic tests of our patient were normal.

Kallabi et al. reported a patient with a poor school performance, reduced concentration, impaired memory and behavior, psychomotor retardation, hearing loss, anorexia, headache, hyperpigmentation, atrophy of the hand and the foot when he was 11 years old.\textsuperscript{12} This case was adolescent cerebral form of ALD similar to our case.

The majority of the mutations in \textit{ABCD1} gene are point mutations, but large deletions had been described in the literature. Shimozawa et al. analyzed the ALD database and reported that 1084 \textit{ABCD1} gene mutations have been updated which included 51% missense mutations, 11% nonsense mutations, 28% frame-shift mutations, 6% amino acid insertions/deletions and 3% one or more exon deletions.\textsuperscript{13} Kok et al. reported deletions between exons 3 to 10, 7 to 10 and 8 to 10 respectively with adrenomyeloneuropathy, cerebral and addison form of the disorder.\textsuperscript{14} Kemp et al. analyzed 406 \textit{ABCD1} gene mutations and reported that no correlation between genotype and phenotype was evident in ALD.\textsuperscript{15}

Genetic counselling and screening families is important in order to detect individuals at risk, including heterozygous women, boys with adrenal insufficiency and asymptomatic person with normal neuroimaging. All males with \textit{ABCD1} gene mutations require ongoing clinical assessment, serial magnetic resonance imaging studies of the brain and assessment of adrenocortical and hearing functions. All of the male individuals in this family were asymptomatic.

**In conclusion**; hearing loss is relatively common in children. 50% of reported diagnoses had a primary genetic defect. Although poor school performance, attention deficit, behavioral changes, quadriplegia, cerebral ataxia, visual and hearing impairment, adrenal insufficiency are classical clinical findings of ALD, severe deafness can be the initial symptom. Therefore, \textit{ABCD1} gene studies should be performed for the diagnosis of bilateral sensorineural hearing loss.

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Conflict of Interest

No conflicts of interest between the authors and/or family members or members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

REFERENCES


