CASE REPORT

DOI: 10.5336/caserep.2017-57351

X-linked Adrenoleukodystrophy Initially Presenting with Severe Deafness

Pembe SOYLU ÜSTKOYUNCU,[a]
Ahmet Sami GÜVEN,[b]
Aslıhan KİRAZ,[c]
Songül GÖKAY,[a]
Durmuş DOĞAN[d]

Clinics of
[a]Pediatric Nutrition and Metabolism,
[b]Pediatric Neurology,
[c]Genetics,
[d]Pediatric Endocrinology,
Health Sciences University
Kayseri Training and Research Hospital,
Kayseri

Received: 24.07.2017
Received in revised form: 21.09.2017
Accepted: 10.10.2017
Available online: 04.06.2018

Correspondence:
Pembe SOYLU ÜSTKOYUNCU
Health Sciences University
Kayseri Training and Research Hospital,
Clinic of Pediatric Nutrition and Metabolism,
Kayseri, TURKEY
drpembesoylu@erciyes.edu.tr

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

X-linked adrenoleukodystrophy (ALD) is the most common peroxisomal disorder characterized by progressive demyelination of the central nervous system and adrenal insufficiency. Poor school performance, attention deficit, behavioral changes, severe visual and hearing impairment are major clinical findings. Hypoglycemia and/or episodes of salt loss, skin hyperpigmentation, quadriplegia and cerebral ataxia may also occur.[1]

The disorder is characterized by accumulation of very long-chain fatty acids and impaired peroxisomal-oxidation. Wiesinger et al. reported that the degradation of C26:0-CoA esters is as severely impaired as degradation of unesterified very long-chain fatty acids in ALD.[2] The disorder is caused by the mutations in *ABCD1* (ATP-binding cassette (ABC), subfamily D, Member 1) gene.

Plasma very long chain fatty acids (VLCFA), enzyme activities in fibroblasts and/or molecular genetic analysis can be made for diagnosis. White matter involvement is typical in the parietal and occipital lobe in computerize tomography and/or magnetic resonance imaging (MRI).[1,3]

Hormone replacement therapy for adrenal insufficiency, and Lorenzo's oil are some treatment options of the disease. Early hematopoietic stem cell transplantation has been shown to prevent cerebral demyelination.[3]

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.

TABLE 1: Laboratory findings of the patient.

Hb (g/dl)	WBC (mm^3)	PLT (mm^3)	Glucose (mg/dl)	Sodium (meq/L)	Potassium (meq/L)	ACTH (pg/ml)	Cortisol (mcg/dl)	C26 (nmol/mL)
13.4	8240	212000	106	137	3,8	>1250	0.88	2.17

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).

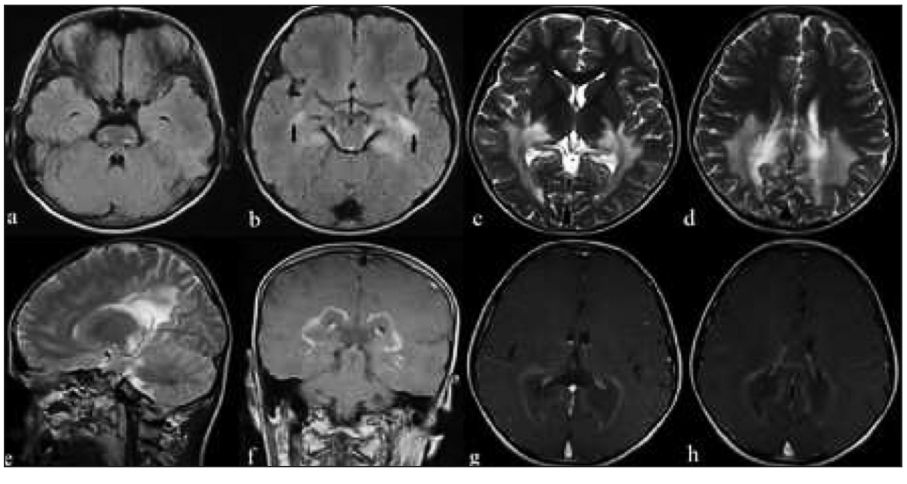

FIGURE 1: The patient's cranial MRI findings. Axial T2-weighted images reveal abnormal hyperintense lesions including bilateral central pons, anterior bulbus, anterior cerebral peduncles, and corticospinal tracts **(a, b)**, Auditory tract and visual tract demyelination involving the region of parietooccipital 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 *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.[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.[6] Late onset Zellweger spectrum disorder (*PEX6* gene mutation), Canavan Disease (*ASPA* gene), Heimler Syndrome (*PEX1* and *PEX6* mutations), Waardenburg syndrome Type-2 (*MITF* gene) and 4 (*EDNRB* gene) should be considered in the differential diagnosis of skin hyperpigmentation and deafness.[7,8]

Mehta et al. reported 612 non syndromic (92.7%) and 48 (7.3%) syndromic patients with sensorineural hearing loss.[6] Usher and Waardenburg syndromes have been identified as the most common causes of hearing loss for syndromic origin. *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.[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.[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.[12] This case was adolescent cerebral form of ALD similar to our case.

The majority of the mutations in *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 *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.[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.[14] Kemp et al. analyzed 406 *ABCD1 gene* mutations and reported that no correlation between genotype and phenotype was evident in ALD.[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 *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, *ABCD1* gene studies should be performed for the diagnosis of bilateral sensorineural hearing loss.

Acknowledgement

All authors thank the patient for participation to this study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family 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.

Authorship Contributions

Idea/Concept: *Pembe Soylu Üstkoyuncu;* ***Design:*** *Pembe Soylu Üstkoyuncu;* ***Control/Supervision:*** *Ahmet Sami Güven;* ***Data Collection and/or Processing:*** *Durmuş Doğan, Songül Gökay, Aslıhan Kiraz;* ***Analysis and/or Interpretation:*** *Durmuş Doğan, Aslıhan Kiraz;* ***Literature Review:*** *Pembe Soylu Üstkoyuncu, Ahmet Sami Güven, Songül Gökay;* ***Writing the Article:*** *Pembe Soylu Üstkoyuncu, Ahmet Sami Güven;* ***Critical Review:*** *Ahmet Sami Güven;* ***References and Fundings:*** *Aslıhan Kiraz;* ***Materials:*** *Ahmet Sami Güven.*

REFERENCES

1. Poll-The BT, Auborg P, Wander RJA. Peroxisomal disorders. In: Saudubray JM, Berghe GV, Walter JH, eds. Inborn Metabolic Diseases: Diagnosis and Treatment. 5th ed. Berlin Heidelberg: Springer-Verlag; 2012. p.592-605.
2. Wiesinger C, Kunze M, Regelsberger G, Forss-Petter S, Berger J. Impaired very long-chain acyl-CoA β-oxidation in human X-linked adrenoleukodystrophy fibroblasts is a direct consequence of ABCD1 transporter dysfunction. J Biol Chem 2013;288(26):19269-79.
3. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy-neuroendocrine pathogenesis and redefinition of natural history. Nat Rev Endocrinol 2016; 12(10):606-15.
4. İncecik F, Hergüner MÖ, Mert G, Önenli-Mungan N, Ceylaner S, Kör D, et al. X-linked adrenoleukodystrophy in a 6-year-old boy initially presenting with psychiatric symptoms. Turk J Pediatr 2014;56(6):651-3.
5. Shimizu H, Moser HW, Naidu S. Auditory brainstem response and audiologic findings in adrenoleukodystrophy: its variant and carrier. Otolaryngol Head Neck Surg 1988;98(3):215-20.
6. Mehta D, Noon SE, Schwartz E, Wilkens A, Bedoukian EC, Scarano I, et al. Outcomes of evaluation and testing of 660 individuals with hearing loss in a pediatric genetics of hearing loss clinic. Am J Med Genet A 2016; 170(10):2523-30.
7. Ong KR, Visram S, McKaig S, Brueton LA. Sensorineural deafness, enamel abnormalities and nail abnormalities: a case report of Heimler syndrome in identical twin girls. Eur J Med Genet 2006;49(2):187-93.
8. Ni C, Zhang D, Beyer LA, Halsey KE, Fukui H, Raphael Y, et al. Hearing dysfunction in heterozygous Mitf (Mi-wh) /+ mice, a model for Waardenburg syndrome type 2 and Tietz syndrome. Pigment Cell Melanoma Res 2013;26(1):78-87.
9. Fasano T, Pertinhez TA, Tribi L, Lasagni D, Pilia A, Vecchia L, et al. Laboratory assessment of sudden sensorineural hearing loss: a case-control study. Laryngoscope 2017;127(10):2375-81.
10. Cabasson S, Rivera S, Mesli S, Dulubac E. Brainstem and spinal cord lesions associated with skin changes and hearing loss: think of biotinidase deficiency. J Pediatr 2015;166(3): 771-1.e1.
11. Moteki H, Azaiez H, Booth KT, Hattori M, Sato A, Sato Y, et al. Hearing loss caused by a P2RX2 mutation identified in a MELAS family with a coexisting mitochondrial 3243AG mutation. Ann Otol Rhinol Laryngol 2015;124 Suppl 1:177-83.
12. Kallabi F, Ben Salah G, Ben Chehida A, Tabebi M, Felhi R, Ben Turkia H, et al. A de-novo large deletion of 2.8 kb produced in the ABCD1 gene causing adrenoleukodystrophy disease. Biochem Cell Biol 2016;94(3):265-9.
13. Shimozawa N, Honda A, Kajiwara N, Kozawa S, Nagase T, Takemoto Y, et al. X-linked adrenoleukodystrophy: diagnostic and follow-up system in Japan. J Hum Genet 2011;56(2):106-9.
14. Kok F, Neumann S, Sarde CO, Zheng S, Wu KH, Wei HM, et al. Mutational analysis of patients with X-linked adrenoleukodystrophy. Hum Mutat 1995;6(2):104-15.
15. Kemp S, Pujol A, Waterham HR, van Geel BM, Boehm CD, Raymond GV, et al. ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. Hum Mutat 2001; 18(6):499-515.