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Childhood Cerebral Form of X-Linked Adrenoleukodystrophy: A Case Report

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Abstract: ***X-linked adrenoleukodystrophy (X-ALD) is an inherited peroxisomal disorder caused by a variant of the ABCD1 gene in the long arm of the X chromosome. It is caused by deficiency or dysfunction of the adrenoleukodystrophy protein (ALDP) which inhibits very long-chain fatty acids (VLCFA) breakdown and causes the accumulation of VLCFA in tissues throughout the body, including the neuronal and adrenal tissue. The childhood cerebral form, marked by quickly progressing neurological decline, is the most prevalent phenotype in young boys, linked to significant morbidity and mortality. Herein we present a pediatric patient with this condition.***

Keywords: X-linked adrenoleukodystrophy, X-ALD, adrenoleukodystrophy, cerebral adrenoleukodystrophy, childhood cerebral form

1. Introduction

X-linked adrenoleukodystrophy (X-ALD) is an inherited rare metabolic disorder caused by a pathogenic variant of the ABCD1 gene. ABCD1 gene is located on the q28 band of the X chromosome and encodes for a peroxisomal membrane transporter known as the adrenoleukodystrophy protein (ALDP) which imports saturated very long-chain fatty acids (VLCFA) into the peroxisomal matrix for degradation by peroxisomal beta-oxidation. The lack or dysfunction of the ALD protein, which inhibits VLCFA breakdown and causes VLCFA accumulation in tissues throughout the body, causes X-ALD. [1] It is the most prevalent peroxisomal disease, affecting 1 in 17, 000 births (hemizygous males and heterozygous females) worldwide [2].

In this case report, we present a pediatric patient with this disorder.

2. Case Presentation

In November 2014, an 8-year-old male was brought to the pediatric emergency care service with headache, vomiting, confusion, fatigue, and syncope episodes. After being administered rectal diazepam and kept on observation for two hours, he was then admitted to our service of neuropediatrics. In his past medical history**,** he had two episodes of febrile convulsions at 7 and 22 months old; the brain electroencephalogram (EEG) and computed tomography (CT) scan at the time were normal. Nothing to note in the family medical history.

On admission, his vital parameters were within normal ranges. On inspection, mild hirsutism on the upper and lower extremities was noticed. During the neurological examination, he responded to pain only and presented spontaneous right unilateral Babinski sign, patellar hyperreflexia, horizontal nystagmus, no meningism, and no temperature. The blood biochemical panel at the moment of hospitalization showed no significant alterations, EEG two hours after hospitalization presented diffuse slowing of delta waves, funduscopic examination evidenced papillary stasis at the beginning of papilledema, and brain computerized tomography (CT) scan presented bilateral diffuse temporo-parietal hypodense lesions, free basal cisterns, no lesions in the posterior cranial fossa, no bone lesions (Figure 1).

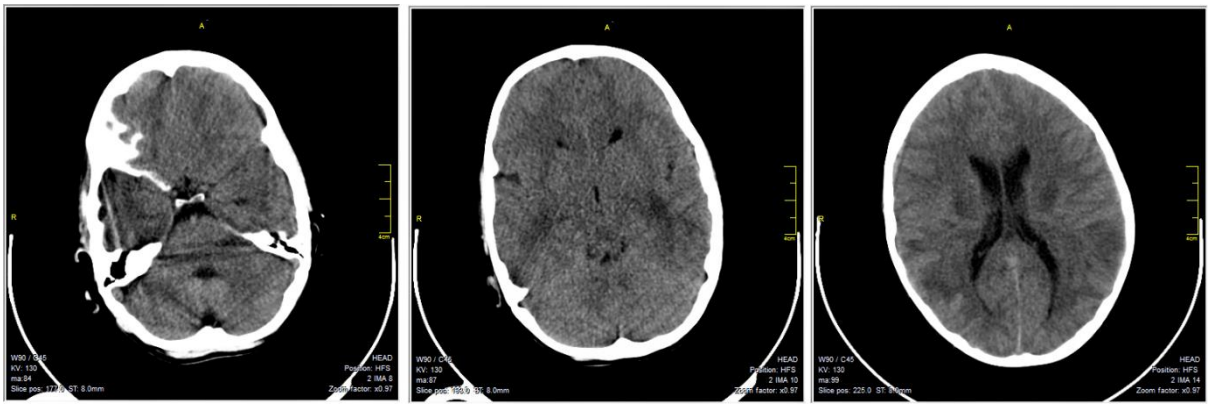

Figure 1: CT scan images in axial projection

Encephalitis was suspected, therefore treatment with piperacillin/ tazobactam 800 mg iv, acyclovir 250 mg iv, dexamethasone 4 mg iv with gradual tapering, mannitol 20% 0-80 mg, furosemide 25 mg iv was started. A few hours after hospitalization the boy had generalized tonic-clonic seizures with perioral cyanosis and eye staring for about 1 minute. Phenobarbital 200 mg iv for 24 hours and valproic acid 300 mg with gradual tapering was added to the therapy. Cerebrospinal fluid examination showed no significant findings.

On hospital day 2, the patient underwent a brain magnetic resonance imaging (MRI) scan with intravenous contrast; there were evident bilateral peritrigonal lesions with hypersignal in T2 and FLAIR extending to the splenium of the corpus callosum and to both lateral lemniscus tracts, peripheral enhancement from intravenous contrast, free basal cisterns, no evident sellar or parasellar lesions, no vascular lesions of the polygon of Willis (Figure 2); leukodystrophy was suspected. Antibiotics and antivirals were interrupted, and he was treated with dexamethasone, valproic acid, and levetiracetam. Laboratory examinations ruled out complete blood count and electrolyte abnormalities. ACTH level was 30.95 pg/mL (normal range 9-52 pg/mL), cortisol level at 08^{00} was 1.20 ug/dl (normal range 5-25 ug/dl). VLCFA profile showed elevated concentration of tetracosanoic acid (C24: 0) and hexacosanoic acid (C26: 0) as well as elevated C24/C22 and C26/C22 ratios, findings consistent with adrenoleukodystrophy. Full-length sequencing of the ABCD1 gene was performed, identifying that the patient is a hemizygous carrier of the pathogenic variant c.1553G>A inherited from his mother. The diagnosis of *X-linked adrenoleukodystrophy* was confirmed. After 15 days of hospitalization, the boy was discharged in good and stable general condition.

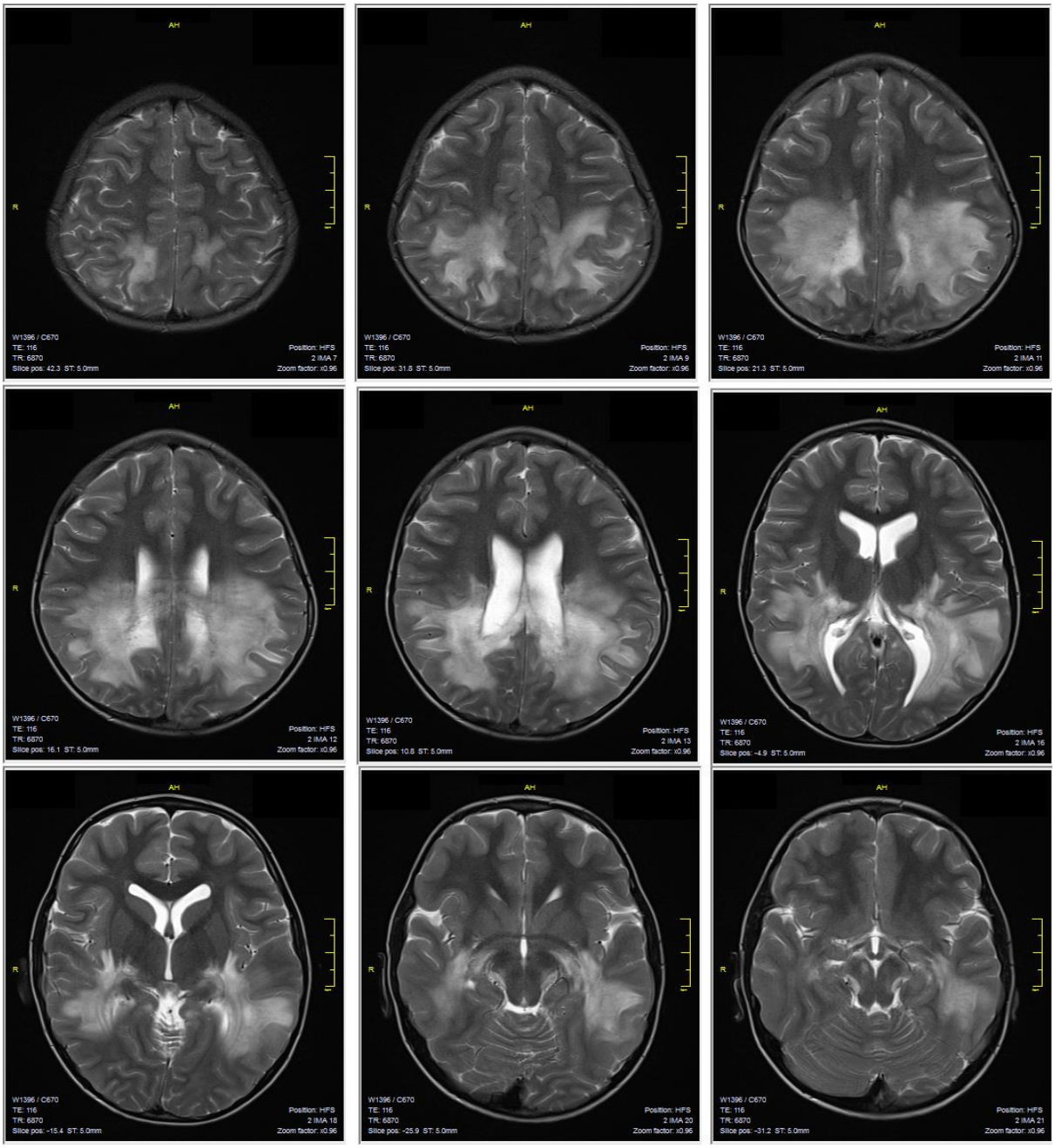

Figure 2: MRI T2 weighted images in axial projection displaying the brain demyelination lesions

In December 2015 (one year later), the child was admitted to our service in a severe condition. He presented with disorientation, vision and hearing loss, and aphasia. He whined and was unable to move, his limbs were contracted, the deep tendinous reflexes were evident, and he had no control over his sphincter muscles. He presented dysphagia as he could only eat soft and liquid food with difficulty; he had lost weight over time. The boy was hospitalized for 7 days and treated with baclofen 10 mg per day, deltacorten 5 mg per day, levetiracetam 2 x 250 mg per day, analgesic, and Lorenzo's oil. He was discharged in stable condition.

To date, the boy is 16 years old, lives in a vegetative state, and is fed through a nasogastric tube (Figure 3).

Figure 3. The current condition of the patient: vegetative state (images from 2020)

3. Discussion

X-linked adrenoleukodystrophy is the most common peroxisomal disorder, present in all regions worldwide. While the majority of patients inherit the ABCD1 gene variant from one parent, de novo mutations have been documented in 4.1% to 19% of the cases [3]. As of November 2022, the ABCD1 Variant Database (www.x-ald.nl) catalogs more than 1040 unique ABCD1 variants that conform to the nomenclature recommended by the Human Genome Variation Society. Our patient's variant is c.1553G>A, and according to ABCD1 Variant Database, it is identified in 52 ALD cases. Other details are presented in Table 1.

X-ALD manifests as a heterogeneous disorder, showing various clinical phenotypes in males and females. In males, it can manifest as the childhood cerebral form, the adolescent form, adrenomyeloneuropathy, the adult cerebral form, the olivo-ponto cerebral form, and Addison's disease only [4]. The presented case is the *childhood cerebral form* of X-ALD known as cerebral adrenoleukodystrophy (CALD); it is the most common phenotype and the most severe, it usually appears in mild childhood, and it is characterized by rapidly progressive neurodegenerative decline, leading to a vegetative state and then death within approximately 4 years after the onset of symptoms [5, 6]. Large-scale analyses have evidenced that there is no general genotype-phenotype correlation. Our patient is an unusual case; regardless of the rapid progress of the disease and the current vegetative state, he continues to live to the age of 16 years.

Table 1: Details regarding our patient's variant

Variant coordinates	c.1553G>A
Type of variant	missense
Chromosome position*	153005610
Amino acid change*	p. Arg518Gln
Exon*	exon 6
Classification ACMG	pathogenic
Status	inherited
ACMG, American College of Medical Genetics and Genomics * as displayed in ABCD1 Variant Database	

The diagnosis of X-ALD is confirmed only by molecular examination which identifies the gene variant, as occurred in our case. It is supported by history, laboratory findings such as ACTH and cortisol levels, very long-chain fatty acids (VLCFA) levels, and magnetic resonance imaging (MRI) which is the golden standard to detect cerebral lesions. In

approximately 80% of cases, brain involvement begins in the splenium of the corpus callosum and then involves the nearby parieto-occipital white matter. Lesions initially affect the pyramidal tracts in the pons or internal capsule and progress to the white matter of the semioval center [7]. Our patient's history, laboratory and imaging findings were typical of CALD.

To date, the allogeneic hematopoietic stem cell transplant is the only treatment that can stop demyelination which is the hallmark of the cerebral forms of the disorder in its early stages [8]. Other therapeutic options have been studied. Lorenzo's oil, a solution of 4 parts glycerol trioleate and 1 part glycerol trierucate, lowers the concentrations of VLCFA in the plasma but has no effect on the endocrinological or neurological function of the patients as it does not improve adrenal function nor does it stop the neurological degradation [9, 10]. Lovastatin leads to an insignificant decrease in levels of C24: 0 and C26: 0 in plasma but does not improve clinical variables [11]. Lastly, Elivaldogeneautotemcel (known as Skysona, Lenti-D, eli-cel) is a gene therapy developed for the treatment of CALD in patients less than 18 years of age, with an ABCD1 genetic variant, and for whom a human leukocyte antigen (HLA) matched sibling hematopoietic stem cell donor is not available. It was granted orphan drug, rare pediatric disease, and breakthrough therapy designations by the U. S. Food and Drug Administration (FDA), and in September 2022 it was granted accelerated approval [12].

4. Conclusion

X-linked adrenoleukodystrophy is the most frequent peroxisomal disease, with varying clinical phenotypes in male and female individuals. The childhood form is the most common phenotype in young boys, associated with severe morbidity and mortality, characterized by rapidly progressive neurodegenerative decline. Awareness and early diagnosis are significant for the progress of X-ALD, particularly when hematopoietic stem cell transplant is considered as a therapy option.

Acknowledgments

Informed consent was obtained from the parent of our patient for the publication of this report.

Conflict of interests

No conflict of interest is declared.

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