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Case Report

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A Case of Adult-Onset Adrenoleukodystrophy with Rare Genetic Mutation

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ABSTRACT

Introduction: Adrenoleukodystrophy (ALD) is an X-linked disorder with a heterogeneous clinical presentation. It is caused by mutations in the *ABCD1* gene, resulting in the accumulation of very long-chain fatty acids (VLCFAs).

Case Report: A 30-year-old male presented with gradually progressive cognitive decline with extrapyamidal involvement. Magnetic resonance imaging revealed white matter signal abnormalities, and genome sequencing identified a rare pathogenic variant in the *ABCD1* gene, confirming the diagnosis of ALD.

Discussion: Our case presented with gradually progressive psychiatric symptoms followed by cognitive, interpersonal and social decline with extrapyramidal involvement. On the basis of MRI brain findings and rare genetic mutation on whole exome sequencing, diagnosis of ALD made.

Conclusion: Adult onset ALD presented with uncommon extrapyramidal symptoms and rare genetic mutation.

Key Words: Adrenoleukodystrophy, Adult-onset, Rare genetic mutation, *ABCD1 Gene*, MRI brain findings, Psychiatric symptoms

INTRODUCTION

Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder caused by mutations in the *ABCD1 gene*, resulting in the accumulation of very long-chain fatty acids (VLCFAs). The first published case of X-linked adrenoleukodystrophy was likely described by Haberfeld and Spieler in 1910. Siemerling and Creutzfeld provided the first detailed description of the disease in 1917, highlighting adrenocortical atrophy, cerebral demyelination, and lymphocytic infiltration.[1] X-linkage was proposed in 1963 through pedigree analysis, and the term "X-linked Adrenoleukodystrophy" was coined by Michael Blaw in 1970.[2] The presence of lipid inclusions in adrenal cells of X-ALD patients, observed by Powers, Schaumburg, and colleagues, led to the discovery of the characteristic accumulation of very long chain fatty acids (VLCFA).[3] The condition manifests variably in males, ranging from childhood cerebral leukodystrophy characterized by cognitive decline and seizures to adult-onset myeloneuropathy, presenting with spastic paraparesis and adrenal insufficiency. These distinct clinical syndromes underscore the heterogeneous and progressive nature of ALD.[4,5]

CASE REPORT

The patient is a 30-year-old married male barber with no prior psychiatric history. He was well two years ago, when he began exhibiting psychiatric symptoms, including excessive talkativeness, verbal abuse toward relatives, and episodes of physical aggression. These symptoms led to hospitalization, where he received treatment for the same with satisfactory initial response. However, over the past 3–4 months, he had experienced progressive cognitive and social decline, accompanied by deteriorating motor function. These symptoms include a slow walking gait, difficulty in turning, rigidity, and reduced speech output. For the past one month, he has been bedridden due to generalized rigidity, displays a fixed staring gaze, and has lost bowel and bladder control. There is **no history of** hallucinations, delusions, seizure-like activity, or REM sleep behaviour disorder.The patient has consumed alcohol almost daily for the past 6–7 years and reports recurrent falls over the last 3–4 years.**Investigation includes** elevated serum total cholesterol (280 mg/dL), elevated LDL cholesterol (189 mg/dL). Complete blood count, liver, renal, thyroid function tests within normal limits. Serum vitamin B12 and folic acid level within normal limit. Serum adren-

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ocorticotropic hormone (ACTH) and cortisol levels were within normal limits. Peroxisomal fatty acid profile was not performed.Ultrasonography whole abdomen was normal. Cerebrospinal Fluid – Protein (120 mg/dL), Cell count (02 cells/dL), Glucose (79 mg/dL), negative for cytology, oligoclonal bands, culture, and Epstein–Barr virus DNA PCR. Urine toxicologic examination negative for common recreational drugs and heavy metals. MRI Brain on axial FLAIR sequence showed symmetrical areas of hyperintensities in the sub cortical white matter in frontal and Parieto-occipital region. (Figure1). Genetic test with whole exome sequencing detected a hemizygous 3' splice site variant in intron 5 of the ABCD1 gene (chrX:g.153740090A>G; Depth: 53x) that affects the invariant AG acceptor splice site upstream of exon 6 (c.1489-2A>G; ENST00000218104.6). (Table 1)

Table 1: HGVS Nomenclature

- Genomic level (GRCh38 assumed): NC_000023.11:g.153740090A>G
- Coding DNA level (transcript ENST00000218104.6 / NM_000033.4): NM_000033.4:c.1489-2A>G

Explanation:

- g.153740090A>G: Substitution at position 153,740,090 on chromosome X from A to G.
- c.1489-2A>G: Substitution two nucleotides upstream of coding position c.1489 (in intron 5), affecting the canonical AG acceptor site just before exon 6.

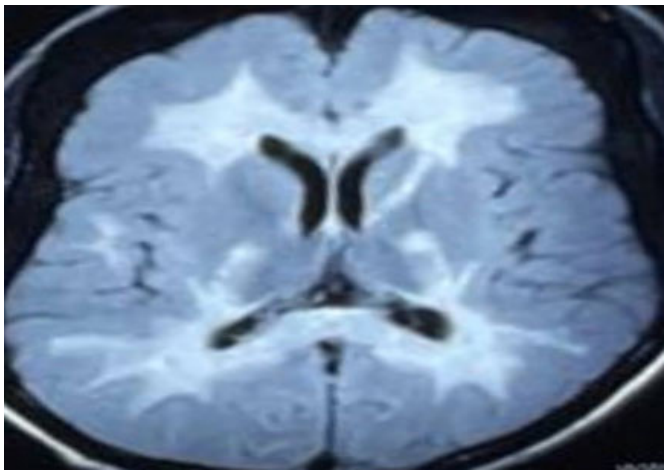

Figure 1: Axial FLAIR showing symmetrical areas of hyperintensities in the sub cortical white matter in frontal and Parieto-occipital region.

DISCUSSION

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder, present in all regions worldwide. It is caused by a mutation in the ATP-binding cassette transporter *D1 (ABCD1) gene* in the Xq28 chromosome. The disease manifests in several distinct phenotypes, with no established genotype–phenotype correlation. Adrenoleukodystrophy (ALD) is classified as the following: childhood cerebral phenotype (48%), adolescent cerebral phenotype (5%), adult cerebral phenotype (3%), adrenomyeloneuropathy (AMN) (25%), and isolated adrenal insufficiency (10%).[6] Our patient a young male presented with gradually progressive psychiatric symptoms followed by cognitive, interpersonal and social decline with extrapyramidal involvement. X-ALD typically presents as adrenal insufficiency (Addison's disease) in 90% of patients, regardless of neurological involvement, which affects 50% of males. Neurological symptoms usually start between three to ten years of age and include attention deficit, developmental regression, spasticity, cortical blindness, cognitive decline, total disability, and death. In adults with late-onset X-ALD who do not show typical childhood symptoms, symptoms may include dementia and behavioral changes, though extrapyramidal symptoms are rare.[7] Adult-onset ALD can present with a variety of symptoms affecting the adrenal, gonadal, neurological, or psychiatric systems. Neurological involvement is common, with gait disorders and upper motor neuron signs often being initial symptoms. Neuropsychiatric symptoms such as disinhibition, emotional lability, increased spending, irritability, and psychosis can also occur. These symptoms may be mistaken for bipolar disorder due to their similarity to manic states.[8] Initial differential diagnosis included alcohol-related neurological disorders. However, further examination and imaging revealed leukodystrophy. Brain imaging revealed diffuse demyelination, leading to a diagnosis of cerebral form of ALD based on clinical features and genetic testing.[9] Majority of patients inherit the *ABCD1 gene* variant.[10] Our patient's variant is c.1489-2A>G, 3' splice site variant in intron 5 of the *ABCD1 gene*. According to ABCD1 Variant Database, it is identified in only one ALD case till now in a 35-year-old African American man with a history of alcohol abuse presented with personality changes and lower extremity weakness. Diffuse demyelination was found on the brain image, and a diagnosis of the cerebral form was made based on the clinical features and genetic test.[11] **Splice Site** mutations occur at the boundaries between exons and introns in a gene, disrupting the process of splicing where non-coding introns are removed from pre-mRNA to create mature mRNA. [12] The "c.1489-2A>G" mutation in the *ABCD1 gene* is a splice site mutation that can lead to Adrenoleukodystrophy (ALD). This specific mutation affects the splicing of the *ABCD1 gene's* pre-mRNA, potentially causing abnormal protein production and contributing to the development of ALD. [13] In our case Peroxisomal fatty acid profile not done as MRI brain and clinical features are suggestive of ALD, so genetic test ordered. In most of the 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 centrum semiovale.[14] In our patient the MRI finding was similar with bilateral parieto-occipital almost symmetrical hyperintensities with involvement of corpus callosum and internal capsule. MRI whole spine was normal. Leukodystrophies typically present in childhood, but late-onset cases can have atypical symptoms and a more gradual progression, leading to delayed diagnosis.[15]

CONCLUSION

Adrenoleukodystrophy (ALD) is a genetic disorder caused by mutations in the *ABCD1 gene,* leading to the buildup of very long-chain fatty acids (VLCFAs). A young male presented with progressive psychiatric symptoms in the form of excessive talkativeness, verbal abuse toward relatives, and episodes of physical aggression along with cognitive decline and extrapyramidal involvement. MRI brain showed symmetrical hyperintensities in subcortical white matter in frontal and parieto-occipital regions with normal serum cortisol and ACTH levels. On Whole exome sequencing a rare mutation in *ABCD1 gene* detected, hence reported.

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