CASE REPORT

Adrenoleukodystrophy: A Rare Clinical Scenario

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Received on: 19 May 2023; *Accepted on:* 17 August 2023; *Published on:* 03 January 2024

Abstract

Background: Adrenoleukodystrophy is a genetic disorder involving the peroxisomes, that leads to defects in beta-oxidation and collection of very long-chain fatty acids. Blaw, in the year 1970 for the first time introduced the term "adrenoleukodystrophy" as a distinct disease with X-linked inheritance and thought to be a metabolic disorder due to enzymes affecting both the adrenal cortex and cerebral white matter. Presently, it is known to be caused secondary to a defect in *ABCD1*gene on *X q28* (ATP - binding cassette, subfamily D [ALD], member 1) gene that results in a defect in peroxisomal beta-oxidation.

Aim: To highlight the rare clinical presentation of adrenoleukodystophy attending to psychiatry outpatient department (OPD).

Methods: A thorough psychiatric history and clinical evaluation, a complete metabolic profiling, and genetic analysis by exome sequencing test to confirm the diagnosis, following MRI findings suggestive of leukodystrophy.

Results: A 14-year-old boy presenting with behavioral abnormality, difficulty in motor coordination, and disinhibited behavior, for about 1 year, presenting to Psychiatry OPD, was found to have white matter hyperintensity suggestive of leukodystophy. A genetic study revealed a hemizygous, pathogenic variant in the *ABCD1* gene, elevation of C26.0 levels, and an increased ratio of C24/22 and C26/22. Later his brother was reported to have behavioral abnormality and was found to have the same genetic findings.

Conclusion: The clinical scenario of ALD can be diverse and confusing. Therefore, keeping in mind the rare possibility will provide genetic testing and further management promptly.

Keywords: *ABCD1* gene, Adrenoleukodystrophy, Case report, Very long-chain fatty acids.

Indian Journal of Private Psychiatry (2024): 10.5005/jp-journals-10067-0157

Introduction

Adrenoleukodystrophy is a heritable condition that affects the peroxisomes and causes abnormalities in beta-oxidation as well as the accumulation of very long-chain fatty acids.[1–4] The very first case of adrenoleukodystrophy was that of cerebral involvement, described in the nineteenth century. Over the years similar cases were described under "Addison–Schilder disease".[5] Due to the lack of any genetic evidence, many similar cases were described as the same. It was also considered a variant of multiple sclerosis. As a separate disease with X-linked inheritance and believed to be a metabolic ailment caused by enzymes affecting both the adrenal cortex and cerebral white matter, Blaw coined the term "adrenoleukodystrophy" in 1970.[5] It is currently understood that it is caused by a defect in the *ABCD1* gene on *X q28* (ATP-binding cassette, sub-family D [ALD], member 1 gene), which results in a defect in peroxisomal beta-oxidation and leads to an accumulation of very long chain-fatty acids (VLCFAs) in a variety of body tissues, including the adrenal cortex, spinal cord, and white brain matter.[6] It has various subtypes depending on the age of onset and also has a range of clinical features that cannot be related to a particular genotype defect. Its course is unpredictable at the time of diagnosis. It mainly affects the nervous system and the adrenal glands.

Case Description

Case 1

A 14-year-old boy with education up to 9th standard of upper-middle socioeconomic status from Puri, Odisha, India presented to the psychiatry outpatient department (OPD). with his parents with complaints of irritability, behavioral abnormality like climbing trees and jumping from a height, disorganized behavior, difficulty in motor coordination, disinhibited behavior, he would watch people while they would change clothes and also had an erratic pattern of sleep. Further, he developed difficulty in concentrating and his parents reported a decline in academic performance over the past 1 year period. The patient was started on treatment with a second-generation antipsychotic and SSRI, but there was no significant improvement for about 2 months. The patient was evaluated for any brain abnormality through electroencephalogram (EEG) and baseline investigations were also performed. No abnormal electrical activity was noted in EEG and all routine investigations were also within normal range. In the next visit, an MRI Brain was advised and it revealed B/L frontoparietal > temporal periventricular white matter hyperintensity with abnormal signals in ganglio-capsulo-thalamic regions suggestive of leukodystrophy, as depicted

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How to cite this article: Kunwar A, Biswal J. Adrenoleukodystrophy: A Rare Clinical Scenario. Ind J Priv Psychiatry 2024;18(1):45–47.

Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient's parents/legal guardians for publication of the case report details and related images.

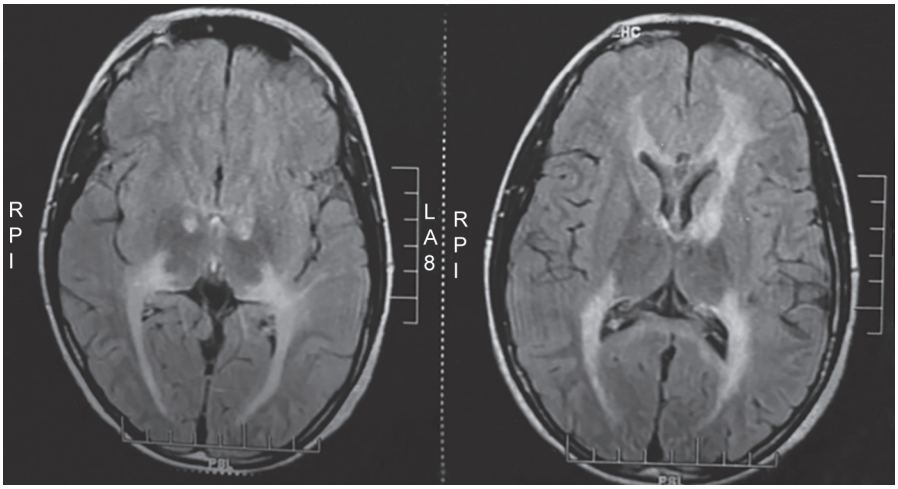

Fig. 1: Case 1 findings

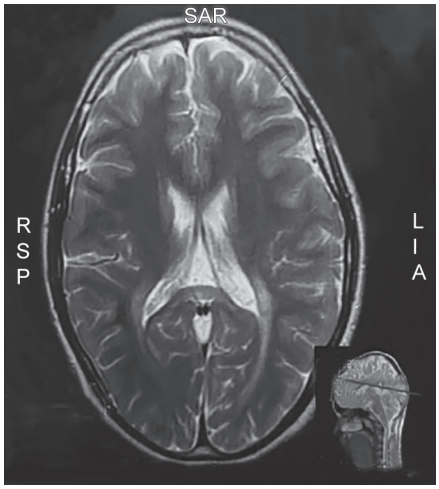

Fig. 2: Case 2 findings

in (Fig. 1). The patient was initially suspected to be affected by adrenoleukodystrophy, metachromatic leukodystrophy, or Alexander's disease.

Investigations for genetic analysis and metabolic profiles were further conducted to confirm the diagnosis. Tandem mass spectrometry revealed no significant abnormality in metabolism and normal activity of enzyme aryl sulfatase A and beta-galactosidase ruling out the possibility of metachromatic leukodystrophy. Further, In a Genetic study through exome sequencing test, a hemizygous c.871G > A (p.Glu291Lys) variant in the *ABCD1* gene was detected, and an impression of XLR X linked recessive; HGVS hg (19): NM_000033.4 (*ABCD1*) was given, the variant was classified as pathogenic. The sample in the stable isotope dilution Gas Chromatography-Mass Spectrometry showed elevation of C26:0 levels and the ratio of C24/22 and C26/22 were higher than normal, findings likely to be suggestive of proximal disorder, with a strong possibility of X-linked adrenoleukodystrophy (ALD) or Adrenomyeloneuropathy. Based on clinical correlation and genetic findings, a diagnosis of X-linked adrenoleukodystrophy was made.

Case 2

The former patient's parent also reported a monozygotic sibling of the patient, a male 14-year-old, who also has mild behavioral disturbances like forgetfulness, poor concentration, and irritability. Magnetic resonance imaging (MRI) findings suggested features of leukodystrophy as depicted in Figure 2 following which a genetic analysis was done in the view of diagnosis for ALD and results reported striking similar findings as reported in the earlier case. Treatment for both patients was focused on symptomatic management. The patient's behavioral disturbances were significantly reduced with tablet Quetiapine (200 mg/day) and tablet Oxcarbazepine (600 mg/day). The patient's parents were psycho-educated about the illness and available treatment modalities were explained. Behavioral management and training were provided to the parents as well as to the patient.

Discussion

The way affected individuals of ALD manifest symptoms are very different. A variety of symptoms present depending upon the involvement of the adrenal gland and central nervous system. CNS and adrenal involvement may be isolated, simultaneous, or sequential. The type of phenotype presented does not correlate with the genotype involved.[7] Clinical subgroups for Addison's disease alone, heterozygous women, presymptomatic variation, adult cerebral ALD, childhood cerebral ALD, and adrenomyeloneuropathy (AMN) have all been identified.[8] In adrenoleukodystrophy behavioral disturbance can be an early presentation. The traditional or childhood-onset variety of ADL is a neurodegenerative illness that manifests as attention deficit disorder, intellectual disability, a number of behavioral abnormalities, and eventual neurological decline. Primary adrenal insufficiency, numerous neurological dysfunctions, and mental disorders are common manifestations of the adolescent-onset type.[9] Few atypical presentations have been noted. An adolescent with ALD, presented only for medical treatment for glue sniffing.[10] Another young kid, age 18, was admitted to the hospital due to progressive body hyperpigmentation, deteriorating vision, and hearing impairment. He later displayed aberrant behaviors and experienced one seizure.[8]

Conclusion

The clinical feature of adrenoleukodystrophy is a constellation of various symptoms, of which behavioral abnormalities remain most consistent. We described a young boy of 15 years of age and his twin brother who presented to Psychiatry OPD with behavioral abnormalities, motor disturbances, and cognitive decline, not fitting into any psychiatric disorder diagnosis. Timely MRI reported the likelihood of leukodystrophy, which later proved to be X-linked recessive adrenoleukodystrophy ALD or adrenomyeloneuropathy on genetic testing. The clinical scenario of ALD can be diverse and confusing. Therefore, keeping in mind the rare possibility will provide genetic testing and further management promptly.

References

1. Weinhofer I, Zierfuss B, Hametner S, et al. Impaired plasticity of macrophages in X-linked adrenoleukodystrophy. Brain 2018;141(8):2329–2342. DOI: https://doi.org/10.1093/brain/awy127.
2. Turk BR, Theda C, Fatemi A, et al. X-linked adrenoleukodystrophy: Pathology, pathophysiology, diagnostic testing, newborn screening and therapies. Int J Dev Neurosci 2020;80(1):52–72. DOI: https://doi.org/10.1002/jdn.10003.
3. Furlan FLS, Lemes MA, Suguimatsu LCF, et al. X-linked adrenoleukodystrophy in Brazil: A case series. Rev Paul Pediatr 2019;37(4): 465–471. DOI: https://doi.org/10.1590/1984-0462/;2019;37;4;00015.
4. Chen Y, Polara F, Pillai A. Rare variability in adrenoleukodystrophy: A case report. J Med Case Rep 2018;12(1):182. DOI: https://doi.org/10.1186/s13256-018-1722-z.
5. Engelen M, Kemp S, Poll-The BT. X-linked adrenoleukodystrophy: Pathogenesis and treatment. Curr Neurol Neurosci Rep 2014;14(10):486. DOI: https://doi.org/10.1007/s11910-014-0486-0.
6. Honey MIJ, Jaspers YRJ, Engelen M, et al. Molecular biomarkers for adrenoleukodystrophy: An unmet need. Cells 2021;10(12):3427. DOI: https://doi.org/10.3390/cells10123427.
7. Wiesinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: Inheritance, mutations, modifier genes, and diagnosis. Appl Clin Genet 2015;8:109–121. DOI: https://doi.org/10.2147/TACG.S49590.
8. Mondol MBA, Siddiqui MMR, Wahab L, et al. Adrenoleukodystrophy : A Rare Case Report. Journal of Bangladesh College of Physicians and Surgeons 2010;28(3):7–10. DOI: https://doi.org/10.3329/jbcps.v28i3.6514.
9. Rosebush PI, Garside S, Levinson AJ, et al. The neuropsychiatry of adult-onset adrenoleukodystrophy. J Neuropsychiatry Clin Neurosci 1999;11(3):315–327. DOI: https://doi.org/10.1176/jnp.11.3.315.
10. Meher RK, Aghoram R, Nair PP. Adrenoleukodystrophy presenting as glue sniffing. BMJ Case Rep 2020;13(3):e233036. DOI: https://doi.org/10.1136/bcr-2019-233036.