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Adult-onset cerebral X-linked adrenoleukodystrophy presenting with frontal lobe syndrome caused by a de novo *ABCD1* gene mutation (c.1415_1416delAG, p.Gln472fs*83)

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X-linked adrenoleukodystrophy is an uncommon genetic disorder characterized by impaired peroxisomal very-long-chain fatty acids (VLCFAs) beta-oxidation.[1–5] Mutations in the *ABCD1* gene on the X chromosome are responsible for X-linked adrenoleukodystrophy. These mutations lead to the absence or dysfunction of adrenoleukodystrophy protein

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Ethics approval and consent to participate

This case report involves a study with human data. The study was conducted respecting the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Formal ethics approval was waived. No reference number was provided, as approval was not required. Informed consent for participation in the study was obtained from the patient. The patient's identity has been protected, and all data presented are anonymized to maintain confidentiality.

Informed consent

Written informed consent was obtained from the patient participating in the study.

Study funding

No specific funding was received for this work.

Conflict of interest

Dr. Ritwik Ghosh (ritwikmed2014@gmail.com) reports no relevant disclosures.
Dr. Moisés León-Ruiz (pistolpete271285@hotmail.com) reports no relevant disclosures.
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(ALDP), a peroxisomal transmembrane protein. ALDP is essential for transporting VLCFA-CoA esters from the cytosol into the peroxisome. This process is crucial for the catabolism of VLCFAs, and its disruption results in the accumulation of these fatty acids, contributing to the pathology of the disease.[1–5]

We report a patient with adult-onset cerebral X-linked adrenoleukodystrophy who presented with frontal lobe syndrome caused by a de novo mutation (c.1415_1416delAG, p.Gln472fs*83) in the *ABCD1* gene representing a novel phenotypic and genotypic variant, respectively.

A 50-year-old male patient from rural India was referred to our clinic in an akinetic-rigid-mute state. He was well two years back. From then, their family members referred progressive behavioral abnormalities in the form of de-pressed mood, diminished interest in pleasurable activities, loss of volition and initiative, feelings of guilt and worth-lessness, significant psychomotor retardation, severe lack of energy, several suicidal attempts, extreme rage, coprolalia, inappropriate jocularity (Witzelsucht), insight impairment, confabulation, utilization behavior and environmental de-pendency, and perseveration suggestive of frontal lobe syndrome. This picture was associated with progressive stiffening of lower limbs, loss of dexterity and clumsiness of upper limbs, and strained speech. Rapid advanced abnormal emotional regulations disrupted social behavior, and personality changes occurred. He also had recurrent unprovoked falls for the last year due to an unsteady gait. For the previous three months, he became bedridden and needed assistance for every daily life activity. One of his younger brothers had died at 45 with a similar neurological illness, which was not documented.

A general examination revealed an emaciated, bedridden individual who required assistance for all sorts of daily life activities. He was pale, had features of chronic malnutrition, and there was uncontrolled emotional and sphincter regula-tion and overt excessive salivation.

On neurological examination, he was mute and had rigidity (inability to relax muscles) and velocity-dependent resistance during muscle tone assessment compatible with paratonia. There were profound global cognitive impairments, apathy, anarthria, pseudobulbar palsy, symmetrical spastic quadriparesis, exaggerated deep tendon reflexes, and bilateral extensor plantar responses.

A complete blood cell count revealed microcytic, hypochromic anemia and neutrophilic leukocytosis with a raised erythrocyte sedimentation rate. Renal function tests revealed low serum creatinine. There was mild hyponatremia, hypokalemia, and mild hypoalbuminemia. Liver, thyroid, and parathyroid function tests were within normal range, and so were glycemic indices. Serologies for HIV (1, 2), hepatitis B and C viruses, John Cunningham virus, and syphilis were negative. Electrocardiography and echocardiography were unremarkable. Contrast-enhanced computed tomography scans of the neck, thorax, and abdomen were unremarkable.

Brain magnetic resonance imaging showed bilaterally symmetrical hyperintense lesions across T1-weighted, T2-weighted fluid-attenuated inversion recovery, and T2-weighted sequences. These lesions exhibited strongly restricted diffusion on diffusion-weighted

imaging and showed patchy contrast enhancement. Affected areas included the subfrontal and periventricular white matter, corticospinal tracts, and cerebellar white matter. Additionally, there was noticeable atrophy of the midbrain, pons, medulla, and cervical spinal cord. These findings were suggestive of adult-onset leukodystrophy (Figure 1).

Due to limited resources at our hospital for measuring plasma concentrations of VLCFAs, whole exome sequencing was initiated. This analysis revealed a hemizygous frameshift mutation representing a novel pathogenic variant in the ABCD1 gene. Precisely, the variant c.1415_1416delAG in exon 5 leads to a frameshift and premature protein truncation at amino acid 472 (p.Gln472fs*83). This mutation is associated with X-linked adrenoleukodystrophy, which explains the clinical presentation observed.

We also evaluated for associated adrenal insufficiency, which was ruled out. Genetic counseling was provided to caregivers and family members, during which the prognosis and implications of the genetic findings were thoroughly discussed.

Only one previously reported possible adult-onset X-linked cerebral adrenoleukodystrophy adult-onset case with frontal lobe dementia has been reported.[6] Still, neither genetic testing nor whole exome sequencing was performed, and therefore, X-linked adrenoleukodystrophy diagnosis could not be confirmed.[6] So, as far as we know, this would be the first reported confirmed X-linked adrenoleukodystrophy case with frontal lobe syndrome as presenting manifes-tation, originated by a de novo ABCD1 gene mutation (c.1415_1416delAG, p.Gln472fs*83), which would constitute a novel phenotypic and genotypic variant, respectively.

It is essential to identify affected individuals with leukodystrophies promptly. However, there is a lack of awareness of these disorders, especially by nonspecific symptom presentation (e.g., cognitive or motor develop-mental delay), and X-linked adrenoleukodystrophy is among these disorders.[7]

In adults, early cognitive decline is rarely recognized by their families and friends or at work.[5] As the disease progresses, psychiatric disturbances mimicking schizophre-nia or psychosis are not infrequent.[5] In those cases, X-linked adrenoleukodystrophy diagnosis is often delayed, mainly when no family history of X-linked adrenoleukodystrophy is present and when clinical symptoms of Addison’s disease are absent (as in our case).[5]

It is important to note that in our case, the brain lesions exhibited significant diffusion restriction, indicative of demyelination and cellular damage within the white matter. Such imaging characteristics are commonly observed in toxic and metabolic leukoencephalopathies. This imaging pattern is somewhat atypical for leukodystrophies, which generally present with different MRI features. This finding underscores the complexity of diagnosing and distinguishing between various types of white matter diseases.[8] Peripheral diffusion-weighted imaging hyperintensities and gadolinium enhancement are observable features in X-linked adreno-leukodystrophy;[9,10] however, significant diffusion restriction should not rule out that entity.

Our case highlights the importance of (1) knowledge regarding phenotypic and genotypic X-linked adrenoleukodystrophy heterogeneity; (2) X-linked adrenoleukodystrophy may present as a frontal lobe syndrome in adulthood; (3) carefully understanding/interpreting neuroimaging characteristics of adult white matter disease patterns; and (4) asking for whole exome sequencing in case of a strong clinical suspicion of X-linked adrenoleukodystrophy for diagnostic confirmation.

Early recognition of frontal lobe syndrome heralding X-linked adrenoleukodystrophy could help achieve a prompt diagnosis, proper supportive management, and genetic counseling. Finally, further prospective and more extensive studies analyzing symptoms and prognosis associated with this novel *ABCD1* gene mutation, including frontal lobe syndrome as a phenotypic marker, are warranted.

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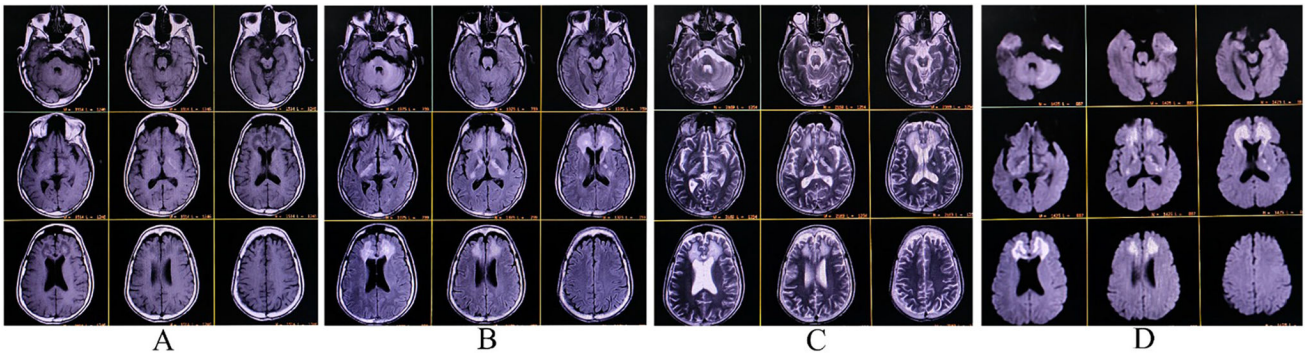

Figure 1.

Magnetic resonance imaging of the brain reveals bilaterally symmetrical hyperintensity lesions on T1-weighted (A), T2-weighted-fluid-attenuated inversion recovery (B), T2-weighted images (C) with areas of strongly restricted diffusion on diffusion-weighted image, which was confirmed on the apparent diffusion coefficient map (not shown) (D) involving sub frontal periventricular white matter, the corticospinal tracts and cerebellar white matter, and atrophy of midbrain, pons, and medulla suggestive of adult-onset leukodystrophy.