Case Report

Role of MRI in X-linked adrenoleukodystrophy—A case report

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A R T I C L E   I N F O

Article history:
Received 8 August 2022
Accepted 16 August 2022
Available online 18 September 2022

Keywords:
Adrenoleukodystrophy
Very long chain fatty acids
X-linked disorder

A B S T R A C T

X-linked adrenoleukodystrophy is a rare inherited peroxosomal disorder that occurs due to a genetic mutation. This mutation impairs normal transport of very long-chain fatty acids (VLCFAs) into peroxisomes, hence impeding VLCFA breakdown leading to its accumulation in plasma and tissues of the body. Due to its X-linked inheritance, it classically affects young males with most cases diagnosed during childhood. There are characteristic MRI findings in brain which can aid in diagnosis of X-ALD. We hereby present a case of a 10-year-old boy who presented with neurological and behavioral deterioration with MRI findings suggestive of X-ALD. MRI not only aids in diagnosis of X-ALD but can also identify the pattern of brain involvement which serves an important role in prognosis and outcome of the disease.

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Introduction

X-linked adrenoleukodystrophy, a metabolic disorder is a rare inherited peroxosomal disorder with an incidence of 1:20,000 in males, that occurs due to a mutation in the ABCD1 gene on the chromosome Xq28, encoding the peroxisomal membrane protein ALDP. This mutation impairs the normal transport of very long-chain fatty acids (VLCFAs) into peroxisomes, hence impeding beta-oxidation and VLCFA breakdown [1]. VLCFAs that is characterized by greater than 22 carbons are thus built up in tissues of the central nervous system, Leydig cells

Abbreviations: ABCD1, ATP Binding Cassette Subfamily D Member 1; ACTH, adrenocorticotropic hormone; ALDP, adrenoleukodystrophy protein; CoA, co-enzyme A; GRE, gradient echo; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; VLCP, very long chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

Competing Interests: The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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https://doi.org/10.1016/j.radcr.2022.08.052
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of the testes, and the adrenal cortex resulting in a variety of clinical symptoms depending on the location of its deposition [2].

The very long-chain fatty acid (VLCFA) panel is very sensitive for diagnosing ALD/AMN in males and is the ideal initial step in the diagnostic process. In males, if VLCFA levels are elevated or VLCFA ratios are abnormal along with either neurological symptoms (with or without MRI abnormalities) or Addison’s diseases, it validates the diagnosis. On the other hand, the VLCFA panel based on free fatty acids is less sensitive in females, as 15% of them have normal VLCFA levels and therefore, genetic testing is the definitive test for female carriers [1].

MRI is of utmost importance in the diagnosis of X-ALD. MRI findings are positive even before the appearance of clinical features in all forms of X-ALD [3]. We hereby present a case of a 10-year-old boy with features of neurological and behavioral deterioration whose MRI findings were suggestive of X-ALD which was subsequently confirmed by the VLCFA panel.

Case report

We present a case of 10-year-old boy with gradually progressive neurological impairment over the last five years. He was

Fig. 1 – (A) T1-weighted MRI image in axial plane shows symmetrical low signal intensities in subcortical and deep white matter of bilateral parieto-occipital lobes, splenium of corpus callosum, posterior limbs of internal capsule and posterior aspect of external capsule. (B) T2-weighted MRI image in axial plane shows symmetrical areas of high signal intensities corresponding to low signal intensity areas in T1-weighted images. (C) T2 FLAIR image does not show suppression of the altered signal intensity areas in T1- and T2-weighted images. (D) GRE images do not show blooming foci in altered signal intensity areas.
delivered vaginally following a full-term pregnancy with no complications. He weighed 2700 grams at birth with APGAR score of 7-9. His symptoms began when he was 5 years old which started with learning difficulties and poor school performance. It was followed by neurological deterioration that included worsening behavioral abnormalities such as easy irritability, inattentiveness, and hyperactivity. His cognitive function was also declining. In addition, there was an onset of visual blurring when he was 9 years old. Recently, he presented to the emergency department of our hospital with two episodes of seizure and abnormal eye movements. Physical examination revealed hyperpigmentation of the skin of chest and axilla. His vitals were within normal limits. Visual acuity testing revealed decreased vision in bilateral eyes. However, on fundoscopic examination, both the optic nerve and retina were normal. At the time of presentation, the patient was alert and oriented but irritated. He could follow simple verbal directions. Spasticity of the limbs was observed with a power of 3/5 bilaterally. The Babinski sign was positive on both sides. The examination of the cranial nerves was unremarkable.

Blood glucose level was found to be 80mg/dl with normal electrolyte panel. Basal 8 am cortisol and ACTH were 3.8 gm/dl (normal range of 5-25) and 2145 pg/dl (normal range of 0-46) respectively which was suggestive of adrenal insufficiency.

His family history includes sudden death of his maternal uncle at the age of 45 due to an unspecified neurological disorder. The patient’s sibling, who is 6 years old, has a reading-based learning impairment.

Fig. 2 – (A & B) T1-weighted MRI image in sagittal plane shows low signal intensity in the splenium of corpus callosum with corresponding high signal intensity in T2-weighted image. (C & D) Postcontrast MRI images in axial plane (C) and sagittal plane (D) show symmetrical serpiginous enhancement in the periphery of the lesion predominantly in the anterior aspect which represents the advancing edge of demyelination which is suggestive of progression of the lesion.
Furthermore, as a part of the diagnostic evaluation, he underwent MRI scan which showed symmetrical pattern of altered signal intensities in bilateral parieto-occipital white matter and splenium of corpus callosum (Figs. 1 and 2). MRS study taken from one of the voxels showed decreased NAA peak (Fig. 3).

Based on the history, laboratory reports and MRI findings, a provisional diagnosis of X-ALD was made. VLCFA was sent for diagnostic confirmation which was found to be elevated. The patient was started on oral hydrocortisone and fludrocortisone and given advice regarding the potential need for a bone marrow transplantation.

**Discussion**

Adrenoleukodystrophy is an uncommon X-linked genetic disorder. X-ALD occurs due to genetic mutation in the ABCD1 gene in the X chromosome that causes dysfunction of a transmembrane protein known as ALDP which transports VLCF acyl-CoA esters from the cytosol into the peroxisome thus preventing normal transport of very long-chain fatty acids (VLCFAs) into peroxisomes, and subsequently beta-oxidation and breakdown of VLCFAs [1]. VLCFA accumulation may be observed in a variety of tissues and body fluids and may be the sole biochemical abnormality [4].

There are several phenotypic classifications of X-ALD based on the symptomatology in children and adults. In males, adrenomyeloneuropathy (~40%-45% of affected individuals); Cerebral ALD in childhood, adolescent, and adult (~35% of affected individuals); and Addison’s only (~10% of affected individuals), are the major phenotypic classification. However, as with many X-linked diseases, female carriers are considered to be asymptomatic but more than 20% of women may develop adrenomyeloneuropathy-like symptoms later in life [5].

Among various phenotypic classifications of male X-ALD, our case was childhood cerebral adrenoleukodystrophy. The childhood cerebral form manifests most commonly between ages 2.5 and 10 years and is characterized by behavioral and cognitive disorders as well as extensive white matter lesions on MRI. It initially presents with deterioration in academic performance due to cognitive deficits in visuospatial and visuomotor functions. An endocrine disorder such as Addison’s disease is often present. With disease progression, more obvious neurologic deficits emerge and subsequently rapid neurologic decline occurs when there is a massive inflammatory demyelinating lesion involving the white matter of the brain [1].

There are five patterns of MRI lesions classified depending on the anatomic location of the first T2 signal hyperintensity. (pattern 1: parieto-occipital white matter; pattern 2: frontal white matter; pattern 3: corticospinal tract; pattern 4: cerebellar white matter; pattern 5: concomitant parieto-occipital and frontal white matter) [6]. These patterns of involvement help in the determination of disease progression and prognosis. Regular MRI follow-up can be done to look for progression or arrest of the disease [1]. In our case, pattern 1 with parieto-occipital involvement was found which is the most common pattern. In MRI, signal alterations might differ depending on the zonal distribution of the damaged white matter. The central zone is hypointense in T1 weighted images and significantly hyperintense in T2 weighted MRI image. The intermediate zone is isointense to hypointense, and the peripheral zone is moderately hyperintense in T2 weighted images [3].
MR spectroscopy in X-ALD reveals signs of neuronal loss manifested by a drop in NAA peak in the central part of the lesion and a decrease in NAA with an increase in lipid/lactate peak in the peripheral region [3]. Similar decrease in NAA peak was observed in our case.

The main metabolic derangement in this condition includes elevation of unbranched and saturated VLCFA such as tetracosanoic (C24:0) and hexacosanoic acid (C26:0) levels. Additionally ACTH stimulation test, ACTH levels and plasma cortisol levels are also performed to look for associated Addisons disease [7]. Genetic testing that is considered the gold standard test could not be performed in our case due to limited resources. However, characteristic MRI findings suggested the diagnosis of X-ALD.

Management of X-ALD depends upon the severity of the disease. Patients with early illness require supportive counseling from parents, teachers, and phycologists for mild intellectual and behavioral impairments. Bone marrow transplantation and gene therapy also have shown therapeutic success in early diseases. However, individuals with extensive cerebral involvement require a multidisciplinary team of physicians from several specialties, including neurology, genetics, psychiatry, endocrinology, speech therapy, ophthalmology, and audiology. Furthermore, the vast majority of patients with severe illness have adrenal insufficiency and require replacement medication [8].

**Conclusion**

X-ALD is a rare genetic disorder that requires advanced diagnostic modalities for confirmation. However, in a resource-limited country like ours, where biochemical tests such as VLCFA panel and genetic testing aren’t available readily, MRI is of utmost importance for the initial diagnosis. MRI not only aids in diagnosis but can also identify the pattern of brain involvement which serves an important role in prognosis and outcome of the disease.

**Patient consent**

Consent from the patient’s mother was taken on written form for case report and using the MRI images in any journal after explaining in her own language.

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