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A Patient in His Early 20s Presenting with Adrenoleukodystrophy and Addison's Disease; A Case Report

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ABSTRACT

Adrenoleukodystrophy (ALD) is an X-linked disorder caused by a hemizygous mutation in the ABCD1 gene. Patients with ALD have central nervous system (CNS) demyelination and primary adrenal insufficiency (PAI). We present a case of a 21-year-old boy with the Addison's disease type of ALD. The patient had hyperpigmentation of the skin for 3 years, body rash, bouts of diarrhoea, gradual weight loss of 21 kg from 60 to 49 kg, and inability to walk for the last 3 months. His labs showed elevated CPK (678 U/L), serum cortisol A.M. (1.5 µg/dL), and ACTH (1774 pg/mL); USG was normal, and contrast-enhanced brain MRI showed abnormal signal areas. Based on the clinical presentation and lab results, he was diagnosed with primary adrenal insufficiency. The patient was discharged and started on prednisolone 5 mg, omeprazole 40 mg, calcium supplements, baclofen 10 mg, and pregabalin 75 mg, and was counselled for regular follow-up. Patients with ALD should be evaluated for PAI for early diagnosis, as it results in a better prognosis of the disease.

Keywords: Adrenoleukodystrophy; Case Report; Hematopoietic Stem Cell Transplant; Primary Adrenal Insufficiency; Very Long Chain Fatty Acids.

INTRODUCTION

Adrenoleukodystrophy (ALD) is an inherited X-linked disorder caused by a loss-of-function mutation in the ABCD1 gene, located on Xq28, which encodes the ATP-binding cassette transporter (adrenoleukodystrophy protein, ALDP). ALDP is expressed on the peroxisomal membrane and is thought to play an important role in the transport of very long chain fatty acids (VLCFA) [1]. A defect in ALDP results in abnormal or absent β-oxidation, leading to VLCFA accumulation in tissues such as the cerebral white matter, spinal cord, and adrenal gland [2]. Patients with ALD are classified clinically, according to age of onset and the presence of neurological complications, into the following forms: primary adrenal insufficiency (PAI), myelopathy, and cerebral ALD (CALD), of which CALD is the most devastating, occurring at 4-12 years of age and carrying a poor prognosis. The risk of adrenal insufficiency varies throughout life and peaks in the first decade, between 3-10 years [3].

The estimated incidence of ALD is 1:20,000-50,000. Although most cases are diagnosed in childhood, a significant proportion manifest in young adults (late 20s) and rarely present with Addison's disease (~10%) [4].

Here we report a young adult with Addison's disease due to ALD in his early 20s, highlighting the importance of considering the association between ALD and PAI.

CASE PRESENTATION

Patient Information

A 20-year-old boy presented to us with knee pain and gradual difficulty in walking for three months. He had generalized skin pigmentation (**Fig. 1**), skin papules (**Fig. 2**), and weight loss from 60 kg to 49 kg. He had recently been diagnosed with a white matter degenerative disorder (leukoencephalopathy) with progressive spastic quadriparesis two months earlier. He had a past medical history of tuberculosis. Family history revealed that his younger brother had epileptic attacks and died at 8 years of age; the patient's maternal relatives also had a history of skin pigmentation and early death, i.e., three of his maternal uncles died at 6, 15, and 10 years of age. The psychosocial history was not significant.

Fig.1 A and B: comparison between after and before pigmentation of skin

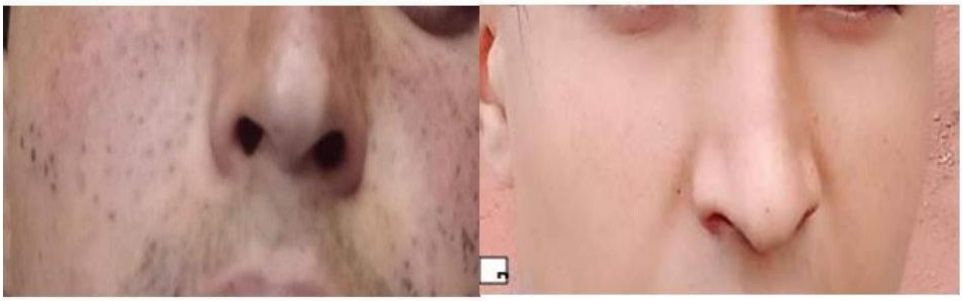
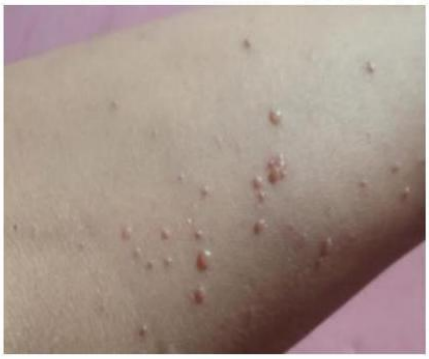


Fig.2: Skin papules on ventral surface of left arm



Physical Examination

On physical examination, his height, weight, and body mass index were 166 cm, 49 kg, and 18.2 kg/m², respectively. His blood pressure was 80/40 mmHg, and he appeared pale. He had decreased sense of position and proprioception and was spastic, while other neurological findings and mental status were normal.

Diagnostic Assessment

EEG and urine investigations were normal, and antinuclear factor (ANF) was negative. Laboratory results are shown in **Table 1**.

Table 1. Baseline laboratory investigations.

Investigation	Result	Reference	Unit
WBC	6.83 ×10³	4-11 ×10³	/µL
Hb	11.7	13-17	g/dL
Na	135	135-145	mmol/L
K	3.70	3.5-5	mmol/L
Cl	102	98-106	mmol/L

Investigation	Result	Reference	Unit
CPK	678	20-200	U/L
ALT	80	7-25	U/L
ALP	29	40-120	U/L
ESR	27	0-15	mm/hr
TSH	2.32	0.4-4	mIU/mL

WBC: white blood cells; Hb: haemoglobin; Na: sodium; K: potassium; Cl: chloride; CPK: creatine phosphokinase; ALT: alanine transaminase; ALP: alkaline phosphatase; ESR: erythrocyte sedimentation rate; TSH: thyroid-stimulating hormone.

Serum cortisol and ACTH were obtained; a comparison between previous (6 months earlier) and latest cortisol and ACTH levels is given in **Table 2**.

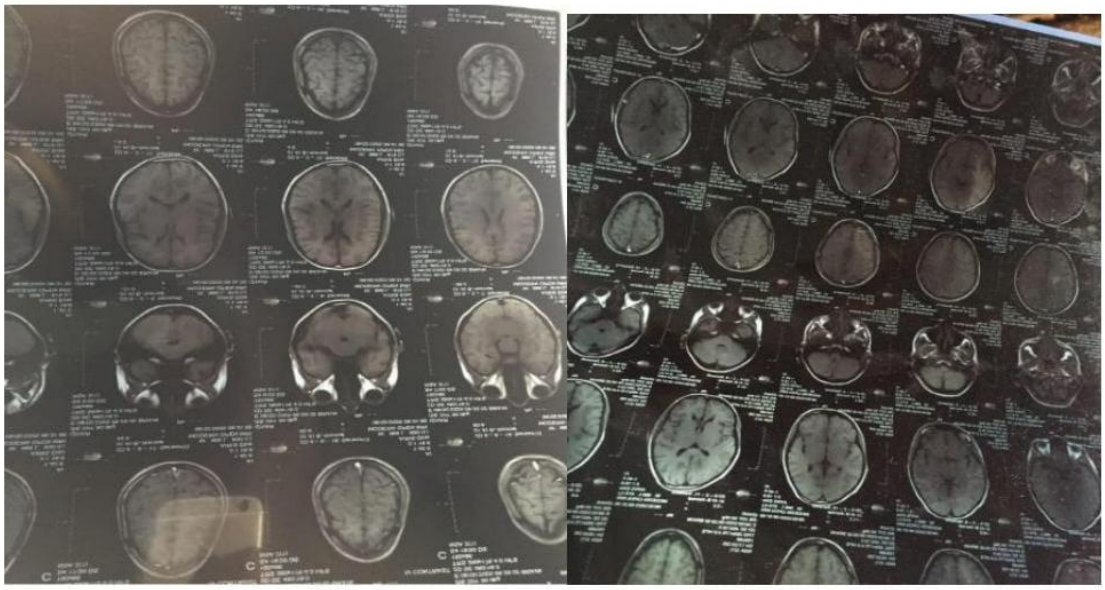
Table 2. Comparison of serum cortisol and ACTH levels.

	Previous	Latest	Unit
Cortisol	1.05	1.5	µg/dL
ACTH	>1250	1770	pg/mL

ACTH: adrenocorticotropic hormone.

Contrast-enhanced MRI of the patient showed an abnormal signal area involving the genu of the corpus callosum, with abnormal high signal extending into the bilateral frontal lobes (lynx sign) (**Fig. 3**).

Fig.3: MRI Film of the patient



We faced diagnostic challenges, as genetic testing and VLCFA measurement could not be performed due to the patient's poor economic status (affordability). The diagnosis of primary adrenal insufficiency was made on the basis of history, examination, and laboratory investigation.

Therapeutic Intervention

The patient was started on prednisolone 5 mg, omeprazole 40 mg, calcium supplements, baclofen 10 mg, and pregabalin 75 mg. He was counselled for regular follow-up. We also faced a therapeutic challenge due to the unavailability of hydrocortisone, which is otherwise effective in PAI, in our area.

Follow-up and Outcome

At the one-month follow-up visit, the patient was responding well but complained of vertigo, so fludrocortisone was added to his previous medications.

DISCUSSION

We report a case of a young adult male with ALD presenting with the Addison's disease phenotype. ALD results from an abnormality of the ATP-binding transport protein, leading to VLCFA accumulation in different tissues; based on the tissues involved, it has various subtypes, each with a varying presentation and prognosis [1]. The main types of ALD are C-ALD, AMN, and PAI-ALD. In C-ALD, the brain in a subset of ALD patients is affected by sub-acute demyelination presenting with psychiatric, behavioural, and cognitive symptoms that progress insidiously and may lead to severe disability or death, most often in childhood; other patients survive C-ALD but progress to severe spinal axonopathy (adrenomyeloneuropathy, AMN), presenting with slowly progressive paraparesis, lower-limb pain, inability to control urine, and male impotence in middle age. The last phenotype of ALD is presentation with only primary adrenocortical insufficiency (PAI), otherwise known as Addison's disease [5,6].

X-linked ALD is a common cause of Addison's disease in boys but is uncommon in adults [7]. Moreover, a retrospective study of 159 patients with ALD showed that the median time to adrenal insufficiency was 14 years (95% CI, 9.70 to 18.30 years) [8]. These observations suggest that PAI may be a major presenting feature in children but only a minor one in adults.

The diagnosis of ALD can be made following clinical suspicion based on neurological symptoms and suggestive family history, biochemical testing for VLCFA, radiological investigation (MRI), and genetic confirmation through DNA analysis of ABCD1 gene mutations [9]. Elevated levels of VLCFA in plasma, skin fibroblasts, and amniocytes are strongly indicative of ALD, without indicating disease type or severity; typical MRI findings (white matter demyelination, microgyria) also play an important role in evaluating ALD [9].

Genetic testing, being the gold standard, is a confirmatory diagnostic test. The ALD database currently lists more than 800 mutations in the ABCD1 gene, without any correlation between the mutation and disease type, except in some rare cases. For PAI-ALD, Addison's disease occurs in the absence of steroid 21-hydroxylase antibodies or any other organ-specific antibodies [3].

Allogeneic haematopoietic stem cell transplantation (HSCT) is the most promising therapy in children with cerebral ALD [10] and has also been tried in young adult patients with cerebral ALD [11]; however, it is not yet known whether it can prevent or rescue other variants of ALD [12]. HSCT has some limitations, as it is not effective in patients with advanced disease; secondly, neurological symptoms present at the time of presentation may not reverse and can progress after HSCT, as stabilization of cerebral disease is achieved only after 3-24 months following stem cell infusion. In addition, finding an acceptable donor, acute mortality associated with HSCT, graft-versus-host disease, and failure of donor cell engraftment are challenges faced in HSCT [3].

For patients with no HLA-matched donor, or adult patients with CALD, haematopoietic stem cell gene therapy with lentivirally corrected cells is the next option; however, the high cost of this procedure, long-term efficacy concerns, and the biosafety of lentiviral vectors should be considered [3].

For X-ALD patients with adrenal dysfunction, glucocorticoid replacement, as in other types of PAI, is essential; mineralocorticoids may not be needed, but in patients with low testosterone and clinical features of hypogonadism, testosterone replacement should be considered, with careful assessment, as impotence may often be due to spinal involvement rather than testosterone deficiency [3].

In summary, children and young adults diagnosed with ALD should also be evaluated for early diagnosis of PAI. Early diagnosis of PAI would allow a more targeted approach and a better disease prognosis. More cumulative data are needed to understand the pathological

events in young adult patients presenting with Addison's disease.

CONCLUSION

ALD can present clinically in multiple forms and with a broad spectrum of symptoms. Although it carries a poor prognosis overall, some forms allow patients to live beyond 65 years with various comorbidities [9]. For prognostic and therapeutic benefit, every patient with primary adrenal insufficiency in early life should be tested for X-ALD.

Informed Consent

Written informed consent for publication of this case report and the accompanying clinical images was obtained from the patient.

Contributors

Dr. Azmat Ali assessed the patient and conceived the case. Mohsin Ali performed the literature review and drafted the manuscript. Sabtain Shah, Muhsin Ali, and Saqlain Shah performed the literature search. All authors critically revised the manuscript and approved the final version.

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Competing Interests

All the authors affirm that they have no conflict of interest.

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