Case Report

A Rare Case of X-linked Adrenoleukodystrophy

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ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is a neurodegenerative disorder caused by an impairment in peroxisomal beta-oxidation of very long straight-chain fatty acids (VLCFAs). Six clinical phenotypes have been delineated: Childhood Cerebral (CCALD), Adolescent Cerebral (AdolCALD), Adult Cerebral (ACALD), Adreno-Myelo-Neuropathy (AMN), Addison-only (AO), and Presymptomatic (PALD). The distribution of phenotypes varies in different countries.

We report the disorder where the diagnosis was made on the basis of clinical spectrum, biochemical analysis and genetic testing.Two siblings presented with skin hyperpigmentation, weakness and nausea, both were diagnosed with Addison's disease and Hypothyroidism. The younger brother later had generalized tonic clonic seizures, abnormal behavior, difficulty in walking, imbalance, intermittent vomiting and difficulty in swallowing. MRI-Brain was suggestive of Adreno-leukodystrophy. The diagnosis was confirmed on genetic testing of ABCD gene mutation.

Key words : Childhood Cerebral (CCALD), Adolescent Cerebral (AdolCALD), Adult Cerebral (ACALD), Adreno-Myelo-Neuropathy (AMN), Addison-only (AO), and Presymptomatic (PALD).

Introduction :

Adrenoleukodystrophy (ALD) is an X linked disorder associated with progressive demyelination of cerebral white matter and adrenal insufficiency. We are reporting this case due to its rarity. The first recorded example of this disorder was by Siemerling and Creutzfeldt in 1923[1]. The first case to be reported in an Indian child was in 1981[2].

There are forty different types of adrenoleukodystrophy (ALD) with a prevalence of 1 in 20,000-50,000 individuals worldwide.[3] This condition occurs with a similar frequency in all populations. People with X-linked adrenoleukodystrophy (X-ALD) accumulate high levels of saturated, very long chain fatty acids (VLCFA) in the brain and adrenal cortex because of impairment of peroxisomal beta oxidation[4,5].

The loss of myelin and the progressive dysfunction of the adrenal gland are the primary characteristics of X-ALD. While nearly all patients with X-ALD suffer from adrenal insufficiency, also known as Addison's disease, the neurological symptoms can begin either in childhood or in adulthood[6]. MRI shows "butterfly-wing" demyelinating lesions at the bi-hemispheric parieto-occipital substance.

The childhood cerebral form is the most severe, with onset between ages 4-10 years. The most common symptoms are usually behavioral changes such as abnormal withdrawal or aggression, poor memory, and poor school performance. Other symptoms include visual loss, learning disabilities, seizures, poorly articulated speech, difficulty swallowing, deafness, disturbances of gait and coordination, fatigue, intermittent vomiting, increased skin pigmentation and progressive dementia[7,8].

ABCD1 (ALDP) maps to Xq28 and its mutation causes X-linked disorder adrenoleukodystrophy (ALD) due to peroxisomal beta oxidation defect, which leads to accumulation of VLCFA , especially the 26-carbon acid, hexacosanoic acid[21]. ABCD1 is a member of the ATP-binding cassette (ABC) transporter superfamily. The superfamily contains membrane proteins that translocate a wide variety of substrates across extra - and intracellular membranes, including metabolic products, lipids and sterols, and drugs. The family also includes ABCC7/CFTR, the gene mutated in the autosomal recessive condition cystic fibrosis[9].

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CASE REPORT:

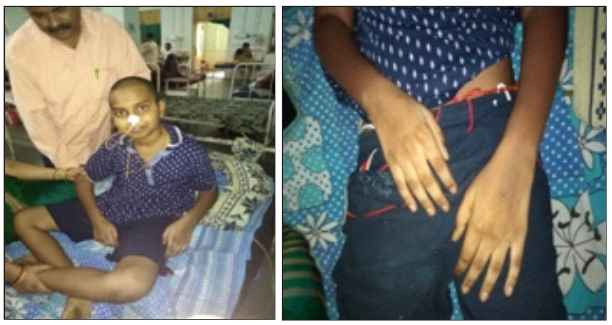
14-year-old boy from non-consanguineous parents, a diagnosed case of hypothyroidism and Addison's disease since 2014, was on regular medication of tablet thyroxin 75 mcg, tablet fludrocortisone 100mcg and tablet hydrocort 10 mg. He presented for recurrent generalized tonic clonic seizures, altered behavior and mild cognitive impairment. He also had progressive darkening of the skin, chronic fatigue and anorexia. He had a similar history of generalized tonic clonic seizures for the first time ten months back, for which he was hospitalized in district hospital. The plain CT head was suggestive of subcortical white matter edema in left parieto temporo-occipital region, Na = 120 meq/lt, K = 4.1 meq/lt, serum ionic calcium = 0.96 (1.01-1.40), BP-90/60 mmHg. He was then discharged from the hospital after control of seizures on antiepileptic drugs and was advised to follow-up with MRI Brain. He had a repeat bout of seizures 6 months and again 2 months back. Repeat CT Scans were suggestive of of ill defined hypodensities along the area of left lateral ventricles. He was advised to undergo an MRI Brain for which he was referred to Government Medical College, Nagpur.

On Examination he was conscious, afebrile, Pulse 88/min regular, BP 110/80 mmHg, RR 14/min, weight 39 kg, height 140 cm, BMI 19.9, He had generalised skin pigmentation along with knuckle pigmentation and hyperpigmentation of gums, no obvious thyroid swelling was present, spine examination was normal. CNS examination revealed mild cognitive impairment with paucity of movement on right side of the body. Sensory system was normal. Other systemic examination was normal.

On laboratory evaluation haemoglobin was 11.2 gm% MCV-102, peripheral smear showed macrocytes and macroovalocytes. KFT & LFT were normal. Serum phosphate-High value, Serum calcium - 8.5 meq/lt, Serum Uric acid - 2.4 mg%. Serum Triglycerides were 145 mgm%, Total cholesterol was 235 mgm%, HDL 54 mgm%, LDL 142 mgm%. Serum TSH 11.7 miu/ml (0.3-5), T4 - 0.91 ng/dl (0.8-2), T3 - 205 ng/dl (82-213), Serum cortisol below 0.4 ug/dl (3-21), Serum ACTH level 1250 pg/ml (10-46). HbA1c was normal, Serum Vitamin B12-310 pg/ml (187-883). ECG, X-Ray Chest & USG Abdomen were - WNL. Fundus examination and CSF were WNL. Serum PTH, anti TPO AB, anti parietal cell AB and VLCFA couldn't be done due financial constraints.

MRI Brain showed predominantly symmetrical areas of altered signal intensity involving bilateral temporo-parietal-occipital, periventricular and subcortical white matter, cerebral peduncles, ventral brainstem, splenium of corpus callosum - features suggestive of adrenoleukodystrophy.

Diagnosis of Adrenoleukodystrophy was further confirmed by Genetic testing of ABCD 1(+) gene located on Exon 6 of variant c.1553G>A (p.Arg 518 GIN) of hemizygous variety with x linked inheritance.



Patient showing knuckle pigmentation

Lorenzo Oil

Patient was managed symptomatically during the hospital stay to control seizures with anticonvulsants, general nursing care, physiotherapy, statins and hormone replacement with thyroxin and steroids. The patient was clinically stable during the hospital stay. Lorenzo's oil a combination of 4:1 oleic acid and erucic acid designed to normalize the accumulation of the very

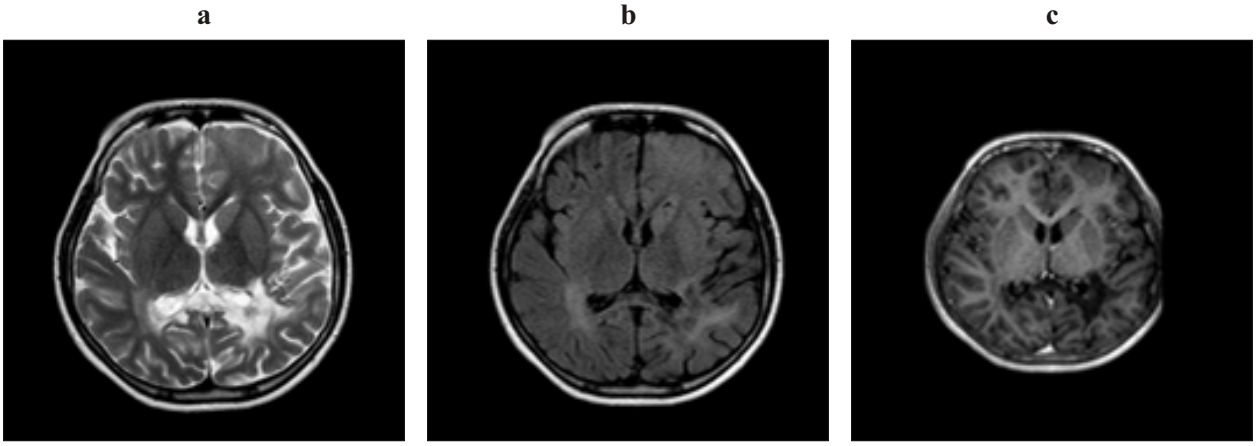
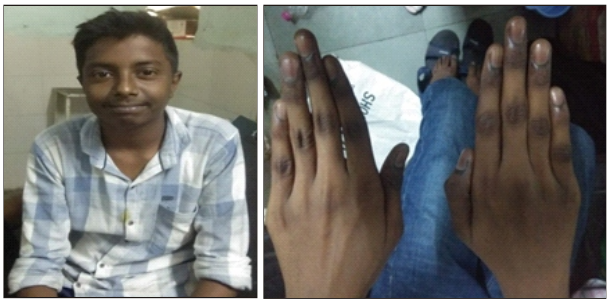


Figure 1 : **a) and b) Axial T2W and FLAIR MR images demonstrate confluent hyper intense signal areas in splenium of corpus callosum and bilateral parieto-occipital deep periventricula white matter with sparing of subcortical U fibers. c) Contrast enhanced MR image shows subtle peripheral enhancement, a finding that is characteristic of Adrenoleukodystrophy.**

long chain fatty acids in the brain and slow the progression of ALD was made available by importing from US.

Patient's 18-year-old elder brother also has progressive darkening of skin, more on sun exposed parts, chronic fatigue and anorexia. He is also a diagnosed case of hypothyroidism with Addison's disease and is on regular replacement therapy since 2014. He was also found to be positive for ALD on genetic evaluation. He has been advised to be referred to higher center for Haematopoeitic bone marrow transplant.



Elder brother showing generalized skin hyperpigmentation and knuckle pigmentation.

Discussion :

Cerebral ALD (childhood, adolescent)

Most frequently present in childhood (childhood cerebral ALD; CCALD), however never before the age of 2.5 years,[10] is the most rapidly progressive and devastating phenotypes of X-ALD[11]. The onset of CCALD is insidious, with deficits in cognitive abilities that involve the spatial and motor visual functions or attention and reasoning,[10] these early clinical symptoms are often misdiagnosed as attention deficit hyperactivity disorder and can delay the diagnosis of CCALD.[12]

The clinical course in adrenoleukodystrophy is characterized by behavioral disorders, ataxia, visual loss, decreased hearing, and epileptic seizures, followed by mental deterioration, psychosis and death. Adrenal insufficiency is a usual finding, but does not always precede neurologic disease[13,14]. Abnormal skin pigmentation and other features of adrenal insufficiency may become apparent before neurological symptoms. In some cases adrenal symptoms may never appear.[15]

Most patients with primary Addison"s disease have darkening of skin, including areas not exposed to the sun. Characteristic sites are skin creases (e.g, of hands), nipple and the inside of cheek (buccal mucosa), new scars become hyperpigmented, whereas older ones do not darken. This occurs due to the excess ACTH stimulation of melanocytes. MSH and ACTH share the same precursor molecule, Propiomelanocortin (POMC).[23,24] The different forms of MSH belongs to a group called the

Melanocortins. This group includes ACTH; alpha, beta, gama-MSH; this peptide are all cleavage products of a large precursors peptide called Propiomelanocortin (POMC). These are produced by the cells in the pars intermedia of the anterior lobe of pituitary gland. Alpha -MSH is the most important melanocortin for pigmentation. Acting through melanocortin 1 receptor, alpha - MSH stimulates the production and release of melanin (a process known as melanogenesis) by melanocytes in skin and hair in response to UV light[25].

Most common cause of primary adrenal insufficiency are either autoimmune adrenal failure (about 75% to 80%) or tuberculosis (about 20%), other etiologies such as ALD are thought to be distinctly uncommon[16]. We should think of ALD when adrenal insufficiency occurs in association with neuropsychiatric manifestations, like in our patient. Demyelination begins bilaterally in the occipital region, extending across the splenium of the corpus callosum. Gradually the process spreads outward and forward as a confluent lesion, affecting the parietal, temporal, and finally, the frontal white matter, cerebellar white matter, cerebellar peduncles, and corticospinal and corticobulbar tracts. Calcium deposition can also be found. MRI is more sensitive than computed tomography to detect these demyelinating plaques. Plain MRI show hypointense signal on T1 and hyperintense signal on T2 and flair images. Post contrast study shows contrast enhancement at the outer margins due to active demyelination and disruption of blood brain barrier[17]. VLCFA can be measured in plasma, which will be raised. Features of primary adrenal insufficiency (Serum ACTH, ACTH stimulation test, Serum. Cortisol, Serum. Testosterone & gonadotropin level) should be measured[18].

Genetic counseling & follow-up of neurologically asymptomatic patients -

Less than 8% of ABCD1 gene mutations are de novo mutations. The mother of an affected boy or adult male has therefore a 92% risk of being heterozygous. A heterozygous X-ALD woman has a 50% risk of giving birth to an affected male. All daughters of an AMN male are obligatory heterozygotes. Once the diagnosis of X-ALD is made in a boy or adult male with X-ALD, and in a symptomatic heterozygous woman who can be the index case of the family, it is crucial to extend the screening of X-ALD to the entire family for the following reasons : (1) to detect women at risk of being heterozygous; (2) to detect neurologically asymptomatic males; (3) to detect X-ALD males who have undiagnosed adrenal insufficiency. Adrenal insufficiency (Addison's disease) is easily treatable but acute adrenal crisis can result in sudden death if not diagnosed[22]. The detection of asymptomatic boys or adult males is crucial for the following reasons : 65% of them are at risk of developing CAD, and there is a treatment available for CAD (see below). However, this treatment can only be proposed at an early stage of cerebral demyelination (in practice, when the patients are nearly asymptomatic). It is therefore highly recommended that all asymptomatic boys or adult males (with or without Addison's disease) should have a brain MRI (with FLAIR sequences) once every 6 months from the age of 4 to 12 years, and then once a year up to the age of 45 years. Up to the time when individual study of genetic variants of normal genes will allow assessment of the risk of developing CAD, this is the only way of detecting CAD at an early stage and saving the patients [22].

Prognosis :

The prognosis of ALD can be estimated on the basis of age and the severity of the brain MRI abnormality, but there are exceptions to these rules, and some patients may remain stable with no further progression for up to 12 years after the initial neurological symptoms[19]. Although childhood cerebral form, causing a severe disability may lead to death early. On the other hand, the adrenomyeloneuropathy is a milder adult form with involvement of mainly the spinal cord and peripheral nerves, having a slow progression with better prognosis.

Treatment :

Treatment is symptomatic, for example, steroid use for adrenal insufficiency and psychotropics for psychiatric symptoms. No clear effective treatments are available, although Lorenzo's oil (4:1

glyceryltrioleate and glycerytrierucate) can be used before the age of 6; it may reduce the probability of developing neurological deficit in late life[18,20]. Statins can reduce VLCFA level, but have no influence in neuronal and endocrine functions[18,20]. Fatty diet should be restricted. Bone marrow transplantation is an option in patient with early neurological features, abnormal magnetic resonance imaging scans and neuropsychological dysfunction. It replaces the blood-forming cells (stem cells) that are missing the important protein with healthy ones. With healthy blood-forming cells, the body is able to break down fat-based substances normally. This keeps the brain, spinal cord and nervous system from more damage. But, it can't fix any damage that has already happened. It is not recommended in the severely affected group and has a significant morbidity and mortality (18,20). As ALD is an X-linked recessive disorder, genetic counseling of family members may be advisable. Early diagnosis also brings the possibility of genetic counseling; carrier detection and antenatal diagnosis and thus we can reduce the incidence of this devastating disease.

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