

**CASE REPORT****Year** : 2018 | **Volume** : 64 | **Issue** : 1 | **Page** : 59-63**Childhood cerebral X-linked adrenoleukodystrophy with atypical neuroimaging abnormalities and a novel mutation****M Muranjan<sup>1</sup>, S Karande<sup>1</sup>, S Sankhe<sup>2</sup>, S Eichler<sup>3</sup>,**<sup>1</sup> Department of Pediatrics, Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India<sup>2</sup> Department of Radiology, Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India<sup>3</sup> Centogene AG, Schillingallee 68, Rostock, Germany**Correspondence Address:**

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India**Abstract**

Childhood cerebral X-linked adrenoleukodystrophy (XALD) typically manifests with symptoms of adrenocortical insufficiency and a variety of neurocognitive and behavioral abnormalities. A major diagnostic clue is the characteristic neuroinflammatory parieto-occipital white matter lesions on magnetic resonance imaging. This study reports a 5-year 10-month old boy presenting with generalized skin hyperpigmentation since 3 years of age. Over the past 9 months, he had developed right-sided hemiparesis and speech and behavioral abnormalities, which had progressed over 5 months to bilateral hemiparesis. Retrospective analyses of serial brain magnetic resonance images revealed an unusual pattern of lesions involving the internal capsules, corticospinal tracts in the midbrain and brainstem, and cerebellar white matter. The clinical diagnosis of childhood cerebral adrenoleukodystrophy was confirmed by elevated basal levels of adrenocorticotropin hormone and plasma very long chain fatty acid levels. Additionally, sequencing of the *ABCD1* gene revealed a novel mutation. The only specific palliative therapy that could be offered after diagnosis was dietary intervention. The patient died within 16 months of onset of neurological symptoms. Awareness that childhood cerebral XALD can present with atypical neuroimaging patterns early in its course may aid diagnosis at a stage when definitive treatment can be attempted and timely genetic counseling be offered to the family.

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**Available from:** <http://www.jpgmonline.com/text.asp?2018/64/1/59/224239>**Full Text****Introduction**

X-linked adrenoleukodystrophy (XALD) is the commonest peroxisomal inborn error of metabolism. The severe phenotype (cerebral form) presents by 5 to 12 years of age.[1],[2],[3] It results from mutations of the ABCD 1 gene on chromosome Xq28 coding for a peroxisomal membrane protein, the ALD protein. Absence of ALD protein impairs peroxisomal oxidation of very long chain fatty acids (VLCFA), resulting in accumulation of hexacosanoic (C: 26) and tetracosanoic (C: 24) acids.[4] The major target organs are the brain, adrenal glands, and testes.[2],[3] Early manifestations include deteriorating scholastic performance, behavior abnormalities, apraxia, astereognosis, word deafness, declining visual acuity, limb paresis, cerebellar ataxia, and seizures.[1] The clinical diagnosis is clinched by demonstration of characteristic patterns of neuroinflammatory white matter lesions on magnetic resonance imaging (MRI) with gadolinium administration accompanied by elevated plasma VLCFA levels. Typical neuroimaging abnormalities in the cerebral childhood form of XALD are parieto-occipital white matter involvement or less frequent frontal white matter lesions.[2]

Loes et al. described a pattern (Pattern 3) involving isolated projection fibers (internal capsule and brain stem) in 15 adults with cerebral XALD.[2],[5] Pattern 3 is an atypical finding in children and has been very rarely reported in asymptomatic and symptomatic children afflicted with cerebral XALD.[2],[5]

Early recognition of such uncharacteristic neuroimaging abnormality is important to suspect this treatable disorder. We describe a child with atypical white matter abnormalities who was confirmed to have cerebral XALD with a novel mutation of the ABCD 1 gene.

## Case Report

A right-handed boy, second offspring of a nonconsanguineous marriage was seen by us at 5 years 10 months of age. Nine months earlier, he had developed behavioral abnormalities (easy irritability, inattentiveness, and hyperactivity), poor speech output, and weakness of the right hand noticed due to difficulty in feeding. Over a period of 3 months, he developed weakness of the right leg leading to frequent falls and deterioration in speech, which was now limited to two- to three-word sentences. Over the next 5 months, symptoms progressed with development of weakness of the left upper and lower limb, resulting in loss of ambulation, inability to stand or sit up in bed, complete loss of speech, dysphagia, drooling, and bladder and bowel incontinence. On enquiry, the parents revealed they had noticed generalized darkening of the skin since 3 years of age. There was no history of deteriorating vision, head trauma, meningitis, measles, or tuberculosis in the past. The boy was born at term per vaginam after an uneventful gestation. Birth weight was 3 kg. He was appropriately immunized. Early milestones were normal.

On physical examination, pulse rate (94/min), respiratory rate (22 breaths/min), and blood pressure (96/68 mm Hg) were normal. The child was undernourished with a weight of 13 kg (<3rd percentile, according to World Health Organization growth charts). The length (111 cm, 15th percentile) and head circumference (50 cm, 50th percentile) were normal. There was generalized melanoderma involving the skin, lips, and buccal mucosa [Figure 1]. The patient was alert and oriented in time, place, and person but irritable. He could obey simple verbal instructions but verbal responses were absent. Other higher functions such as memory and intelligence could not be assessed. Cranial nerve examination was normal. The child was focusing and following light in all four quadrants. The fundus was normal. There was spasticity, which was greater on the right side. Bilaterally, power was 3/5 and deep tendon reflexes were 2+ in the biceps and triceps, 3+ at the knee, and 4+ with bilateral ankle clonus and bilateral Babinski sign. {Figure 1}

Investigations revealed blood glucose of 98 mg/dl, serum sodium of 141 mEq/L, and serum potassium of 4 mEq/L. Adrenal insufficiency was confirmed by basal (8 am) serum cortisol and adrenocorticotropic hormone (ACTH) levels, which were 5.33 µg/dl (normal range 5–25) and 2455 pg/ml (normal range 0–46), respectively. Barium swallow (for achalasia) and Schirmer test (for alacrimia) were normal. Serum and cerebrospinal fluid lactate levels were 6 mg/dl (normal range 4.50–20) and 8 mg/dl (normal range 10–22) respectively.

A retrospective analysis of his two earlier MRI brain was done. The first MRI performed 8 months before admission to our hospital had been reported as leukodystrophy. It revealed bilateral symmetrical T2 hyperintense signal abnormalities involving corticospinal tracts in the ventral pons, cerebral peduncles, sublentiform region, and posterior limb of the left internal capsule [Figure 2]a, [Figure 2]b and [Figure 2]c. The second MRI (performed 3 months before admission to our hospital) revealed a new lesion in the posterior limb of the right internal capsule [Figure 3]a and increase in the extent and signal intensity of the corticospinal tract lesions over the ensuing 5 months [Figure 3]b. Generalized corticocerebral, cerebellar, and brain stem atrophy was also evident [Figure 3]c. MRI brain with intravenous gadolinium administration performed after admission to our hospital revealed further progression with extensive posterior fossa involvement: new lesions were detected in bilateral middle cerebellar peduncles, cerebellar hemisphere, and splenium of corpus callosum [Figure 4]a and [Figure 4]b; lesions in the pons and midbrain were coalescent and minimal patchy enhancement was seen in the posterior limb of the left internal capsule and in the right cerebral peduncle after gadolinium administration [Figure 4]c and [Figure 4]d. There were lipid peaks at 0.9 and 1.3 ppm on magnetic resonance spectroscopy. Elevated plasma VLCFA levels [C26:0 – 2.140 µg/ml (normal 0.23 ± 0.09), C26:1 – 0.5 µg/ml (0.18 ± 0.09), C24:0 – 44.16 µg/ml (17.59 ± 5.36), C24/22 ratio 2.013 (0.84 ± 0.10), and C26/22 ratio 0.098 (0.01 ± 0.004)] confirmed diagnosis of ALD 3 weeks after admission. Analysis of the ABCD 1 gene was performed on high-quality purified DNA. Bidirectional Sanger sequencing was performed with gene and amplicon specific primers using ABI 3730xl sequencer (developed and validated by Centogene AG only for clinical purposes). Reference sequence for ABCD1 gene was NM\_000033.3. Genotyping revealed a novel hemizygous in-frame mutation in exon 1 of the ABCD1 gene (c.257\_268dup, p. Val86\_Arg89dup) [Figure 5]. The family received genetic counseling. An older asymptomatic brother (8½ years old) had normal basal ACTH level (20.4 pg/ml). Carrier testing was advised for the mother but was declined due to monetary constraints (cost for targeted mutation testing: approximately INR 10,000).{Figure 2}{Figure 3}{Figure 4}{Figure 5}

The child was treated with dietary restriction of VLCFA, oral fludrocortisone 50 µg/day, and oral hydrocortisone (10 mg/m<sup>2</sup>/day) in three divided doses. The child was discharged after 47 days of ward stay. At the time of discharge, the child could sit up with support and the pigmentation had reduced. The family did not follow-up after discharge and a phone call to the parents disclosed that the boy had expired in his hometown (16 months after onset of symptoms).

## Discussion

XALD has a spectrum of phenotypes, which includes cerebral ALD (37% childhood onset, 7% adolescent onset, and 3% adult onset), adrenomyeloneuropathy (AMN) (32%), Addison-only disease (13%), presymptomatic disease (7%), and olivo-ponto-cerebellar disease in adolescents or adults (1–2%).[2],[4] Forty percent of patients with AMN have or develop cerebral lesions with inflammatory response and accelerated progression.[6]

Loes et al. have described five MRI patterns in cerebral XALD.[2],[5] The most frequent pattern observed in 66% of cases involves the parieto-occipital white matter and splenium of corpus callosum and includes lesions of the visual and auditory pathway. This pattern usually occurs in children with cerebral ALD.[5] The next commonest pattern (15% of cases) is lesion of the frontal white matter and genu of corpus callosum seen in adolescent-onset disease followed by the pattern seen in 12% of cases, usually in adult-onset disease with involvement of frontopontine or corticospinal projection fibers (internal capsule and brain stem).[5] Enhancement of brain lesions on MRI with gadolinium administration heralds rapid neurological progression as a result of neuroinflammatory demyelination and disruption of the blood–brain barrier.[1]

Subtle abnormal lesions of the pyramidal tract in the brain stem, pons, and internal capsule (similar to the pattern in adults) have been noted in AMN.[1],[7] Pyramidal tract lesions in AMN occur secondary to Wallerian degeneration in patients with longstanding disease.[1] This pattern of pyramidal tract lesions in brain stem, pons, and internal capsule are not considered to be a manifestation of cerebral ALD unless lesions become intense and progress beyond the internal capsule to the white matter of the centrum semiovale.[1],[7] Additionally, central nervous system (CNS) lesions of AMN are not inflammatory and therefore enhancement with gadolinium is absent or mild.

[6],[8]

An adult type of neuroimaging pattern with involvement of projection fibers (internal capsule and brain stem) was detected in our 6-year-old patient with cerebral XALD as the presenting neuroradiological abnormality. As the lesions in our patient demonstrated enhancement with gadolinium (indicating inflammatory nature), they were less likely to be due to AMN. Additionally, the usual age at onset of AMN is >18 years.[1] To our knowledge, the adult pattern of white matter lesions has been very rarely previously reported in children with cerebral XALD.[1],[2],[5] Clinical manifestations in children with lesions involving projection fibers on MRI brain vary from asymptomatic (7-year-old) to behavioral abnormalities (12-year-old), progressive spastic pure motor quadriplegia (9 years old) and regression of milestones, hyperactivity and easy distractibility in a 6-year-old who also had hyperpigmentation and vomiting.[2],[9],[10]

Another unusual feature in our child was the clinical progression with death within 16 months of onset of symptoms despite disproportionately mild neuroradiological evidence of progress to inflammatory phase of the disease as determined by minimal enhancement of MRI lesions and lack of significant anatomical extension rostral to internal capsule.[1],[7] It is possible that the lesions in our child represented an early involvement on the first MRI performed 8 months before admission to our institution. However, as expected in cerebral ALD, the lesions had not progressed to involve white matter of the centrum semiovale on subsequent brain MRI performed after admission to our institution.[4]

Adrenocortical insufficiency precedes diagnosis of cerebral XALD in 65% of cases.[7] On the contrary, in 167 children studied at Kennedy Krieger Institution, 86% had neurological symptoms before signs of adrenal insufficiency.[4] Presence of melanoderma (suggesting adrenocortical insufficiency) in our patient provided us with vital information to suspect XALD even though the MRI pattern was atypical. In the absence of melanoderma, if neuroradiological abnormalities are atypical, like those observed in our patient, diagnosis of XALD could be delayed or missed.

The mutation c. 257\_268 duplication detected in our patient was novel. Because we could not test the mother due to financial constraints, we cannot comment whether this novel mutation was also de novo. Additionally, majority of the families with XALD have private mutations.[4] Possibility of private mutation in our patient cannot be excluded. The mutation in our patient resulted in duplication of four amino acids (valine, leucine, cysteine, and arginine) at positions 86 to 89, respectively, of the ALD protein. This duplication resulted in substitution of glutamic acid at protein position 90 by valine. Missense and frameshift mutations involving glutamic acid at position 90 have been previously reported to be pathogenic.[11] We therefore propose that the mutation in our patient was pathogenic. The pathogenicity of the mutation in our patient was corroborated by the presence of the diagnostic biochemical hallmark of XALD, namely elevated plasma VLCFA. The genotype of our patient may not explain the occurrence of the clinical phenotype of childhood cerebral ALD with atypical neuroimaging patterns as there is no consistent genotype-phenotype correlation in XALD nor is phenotype determined by severity of biochemical abnormalities.[7],[12] Environmental and genetic autosomal modifier loci have been suggested as explanations for the phenotypic diversity in XALD.[3],[7]

Based on clinical features of adrenal insufficiency and neurological abnormalities, differential diagnosis considered in our patient were Allgrove (Triple-A) syndrome (adrenal insufficiency-achalasia-alacrimia with mild dementia, peripheral neuropathy, and cerebellar ataxia), complex glycerol kinase deficiency due to contiguous gene deletion of chromosome Xp21 (adrenal insufficiency, Duchenne muscular dystrophy, hyperglycemia and glyceroluria, with psychomotor retardation) and mitochondrial disorders.[13],[14],[15] These disorders were ruled out by investigations (no lactic acidosis and normal results of barium swallow and Schirmer test).

There are few reports supporting the correlation of symptoms with anatomical lesions on MRI in children.[16] In a series described by Pasco et al., 13 out of 33 children had pyramidal tract signs and pyramidal tract lesions, those with ataxia had cerebellar lesions and behavioral manifestations were observed with frontal lobe involvement.[16] In our patient, the first symptom of localized weakness involving the right upper and lower limb suggested hemiparesis at onset, correlating with the unilateral lesion in the left internal capsule on the first MRI. Such unilateral lesions are described in patients with cerebral XALD triggered by head trauma.[13] In these cases,

demyelination had begun at the site of contusion.[8] In our case, the parents could not recollect any head injury in the child prior to onset of symptoms. Right-side hemiparesis was followed by speech and cognitive impairment and left-side hemiparesis. This bilateral hemiparesis correlated with bilateral involvement of pyramidal tract in the brain stem and internal capsule performed 8 months after the first MRI. However, despite the development of overwhelming CNS symptoms typical of cerebral XALD in our patient (behavioral, speech, and cognitive impairment), there was no corresponding anatomical correlation with widespread involvement of supratentorial white matter on the third MRI. This observation reiterates the lack of correlation between extent and severity of MRI abnormalities and neurological symptoms noted earlier at anatomical sites other than the parieto-occipital white matter.[1]

At the time of admission, our patient was in an advanced stage of the disease with severe neurological symptoms. Hematopoietic stem cell transplant (HSCT) could not be offered in this advanced stage.[1],[6] In conclusion, awareness of uncharacteristic neuroradiological patterns in childhood cerebral XALD may hasten diagnostic evaluation early in the course of the disease and before progression to the neuroinflammatory stage of rapid deterioration. Identification of children in the early stage would give them an opportunity for treatment with HSCT. [12],[17]

#### Declaration of patient consent

The authors certify that appropriate patient consent was obtained.

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#### Conflict of interest

Dr Sunil Karande is the Editor of the Journal of Postgraduate Medicine.

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