Cerebrotendinuous Xanthomatosis: A Treatable Cause of Metabolic Ataxia

AA Mukherjee*, BP Chawla**, SS Rathi+, RS Puthran++

Abstract
Cerebrotendinous xanthomatosis is an exceptionally rare condition in Indian subcontinent, however, it is potentially treatable if diagnosed. We present and discuss the clinical presentation and investigations in a case of cerebrotendinous xanthomatosis (CTX).

INTRODUCTION
Cerebrotendinous xanthomatosis (CTX) is an inborn error of bile acid metabolism. It is extremely rare in Indian population with extremely limited Indian data. Early detection of CTX is crucial as plasma phytosterol can be normalised by drug therapy and that can arrest further damage to nervous system.

CASE REPORT
A 25-year-old man, educated till 7th standard, presented with generalised tonic and clonic convulsions since the age of 5 years. He was on phenytoin therapy which had kept him free from convulsions. Subsequently, he noticed diminished vision, poor scholastic performance and difficulty in balancing while walking. There was no weakness, sensory disturbances or any suggestion of cranial nerve deficits.

He was born of non-consanguineous marriage and the delivery was full-term and vaginal without any neonatal hypoxia or jaundice. There was no family history of similar disorder. Examination revealed bilateral dense cataracts with severely diminished vision (finger counting in the right eye at distance of one meter and 6/60 in left eye). He had nystagmus on left gaze. There was bilateral pes cavus (Fig. 1), bilateral xanthomas affecting achilles tendons (Fig. 2). IQ was assessed by Vineyard Social Maturity Scale and it was 60. Speech was dysarthric. He had generalised wasting of all muscles with significantly more wasting of small muscles of hand and feet. Tone was normal. Power was 4/5 at all joints. Deep tendon reflexes were brisk, however, planters were flexors. He had cerebellar in-coordination, more on the left side. Almost all cerebellar signs were present.

Investigations showed normal haemogram, urine and stool with normal blood chemistry with respect to blood sugar, liver function and renal function. CT scan showed non-enhancing hypodense areas affecting both cerebellar hemisphere together with mild prominence of cerebellar folia and cerebellar atrophy. MRI of brain showed cerebellar atrophy affecting both hemisphere and vermis (Fig. 3). There were bilateral symmetrical focal lesions affecting cerebellar white matter. These lesions appeared hypodense on CT scan. They were slightly heterogeneously hyperintense on T2W images of MRI. On T1W, the lesions appeared hypointense with mildly hyperintense posterior margins (Fig. 3). Changes were more severe in white matter surrounding dentate nuclei. The dentate nuclei themselves appeared more severely involved showing greater hyperintense signals on T2W images. Superior cerebellar peduncles were atrophied. There were no lesions in supratentorial brain parenchyma.

MRI of Achilles tendon showed bilateral asymmetrical soft tissue masses which appear hypodense on T2W images consistent with xanthomas. There was atrophy of brain-stem and the visualized spinal cord. EEG showed generalised hyper-excitability. Lipid studies were normal (Table 1). FNAC of soft tissue masses affecting Achilles tendon showed numerous foamy histiocytes and giant cells amongst a haemorrhagic background.

A diagnosis of cerebrotendinous xanthomatosis was made based on the clinical features, FNAC of the swelling affecting Achilles tendon, findings on CT scan and MRI scan of brain, spinal cord and Achilles tendon.

Patient was treated with chenodeoxycholic acid in the dose of 250 mg 3 times a day together with HMGCoA reductase inhibitor viz. Simvastatin.

DISCUSSION
Patient under discussion had almost all the features of cerebrotendinous xanthomatosis (CTX) described in literature. CTX is a rare autosomal recessive lipid storage disease with prominent neurological features. It was...
first described by Vas Bogaert et al in 1937. Its unique chemical feature i.e. deposition of cholestanol, a derivative of cholesterol within nervous system was uncovered only in 1968 by Menkes et al. Disease is associated with mutations in CYP27, which encodes mitochondrial sterol, 27-hydroxylase, an enzyme that catalyzes oxidation of sterol intermediates during bile acid synthesis. Loss of enzyme results in accumulation of cholestanol in many tissues and particularly in brain. Deficiency of cholic acid and chenodeoxycholic acid occurs.

The clinical features of CTX are depicted in Fig. 4. Cataracts may be the presenting finding in first decade of life

Table 1: Lipid studies

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<tr>
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<td>126</td>
<td>mg/dl</td>
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<tr>
<td>VLDL cholesterol</td>
<td>12</td>
<td>mg/dl</td>
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Fig. 1: Pes cavus deformity and swelling of tendo-achilles due to xanthoma.

Fig. 2: Bilateral swelling of Achilles tendons due to xanthoma.

Fig. 3: MRI: Cerebellar atrophy affecting both hemisphere and vermis. Bilateral symmetrical focal lesions affecting cerebellar white matter which are slightly heterogeneously hyperintense on T2W images and hypointense with mildly hyperintense posterior margins on T1W images.

Fig. 4: Clinical features of cerebrotendinous xanthomatosis.

Table 1: Lipid studies
in 75% of cases. In the remaining, it may develop even after the age of 40 years. Patients develop palpable xanthomas which appear during 2nd or 3rd decade. They are classically seen in Achilles tendon. They may also be seen around elbow, patella, neck muscle tendons as well as affecting CNS, lungs and bones. Premature atherosclerosis and coronary artery disease have been reported. Involvement of bone is characterised by granulomas affecting lumber vertebrae and femora leading to osteopenia and increased risk of pathological fractures. There may be early loss of teeth. This together with early onset of cataracts, atherosclerosis, neurological impairment and fracture of bones are all suggestive of a generalised premature aging process. Patients may also get chronic diarrhoea.

Neurological findings include mental retardation or dementia. There is slow deterioration in intellectual abilities in early 20s in 50% of individuals. Neuropsychiatric symptoms such as behavioural changes, hallucinations, agitation, aggression, depression and suicide attempts are common. Pyramidal signs i.e. spasticity and/or cerebellar signs invariably present by 20 or 30 years of age. A spinal form in which spastic paraparesis was the main clinical feature, has been described. Seizures occur in 50% of individuals and could be a presenting feature of CTX. Extra- pyramidal manifestations include dystonia and atypical parkinsonism. Peripheral neuropathy (PN) can result into atrophy of muscles and pes cavus. PN is evident on electrophysiology studies which reveal decreased nerve conduction velocities (nCV) and abnormalities in sensory, motor, brain stem and visual-evoked potentials.

Investigations show increased cholestanol levels in both serum and erythrocytes. S. cholesterol and triglyceride levels are normal. Neuro-imaging shows changes of cerebral and cerebellar atrophy on CT and MRI. T2 weighted images may show focal or diffuse high signal intensities in cerebral and cerebellar white matter. Dentate nuclei could be hyperintense on FLAIR images. Spinal cord atrophy may be seen. MRI of Achilles tendon shows soft tissue swelling.

Management includes use of chenodeoxycholic acid (CDCA). Clinical improvement following its use in patients of CTX was first reported by Berginer G et al in 1984. Long-term treatment with CDCA in doses of 750 mg/d normalizes bile acid synthesis leading to disappearance of abnormal metabolites from plasma, bile and urine. CDCA normalizes plasma and CSF concentration of cholestanol by suppressing its biosynthesis and this leads to improvement in neurophysiological status. Berginer et al, in a study of 17 patients showed that by the end of one year of treatment with CDCA, 10 subjects cleared their dementia, five patients had disappearance of pyramidal and cerebellar signs while another eight showed improvement. Peripheral neuropathy was no longer detectable in six. EEG became normal in five while CT scan showed improvement in seven. Cerebellar xanthoma disappeared in one. Thus, the treatment with CDCA corrects biochemical abnormalities leading to arrest of progressive disease.

Use of HMG-CoA reductase inhibitors in combination with CDCA is effective in decreasing cholesterol concentration and improving clinical signs. This has been shown by Verrips A et al. Other possible treatment modalities include low density lipoprotein (LDL) apheresis, however, the results are controversial. Most patients require cataract extraction by the age of 50 years. Parkinsonism response poorly to levodopa.

REFERENCES