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Clinico-Radiological Presentation of Cerebrotendinous Xanthomatosis (CTX) in Two Sisters of an Indian Family with Review of Literature

Case Report

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Abstract

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessively inherited, treatable, metabolic lipid storage disorder, presenting with early non-neurological manifestations (intellectual disability, chronic intractable diarrhea, juvenile bilateral cataracts, multiple xanthomata around the eyelids and Achilles tendons, premature atherosclerosis and pulmonary dysfunction) followed several years later by adult-onset neurological dysfunctions (dementia, spasticity, ataxia, peripheral neuropathy) and neuropsychiatric symptoms. We are presenting two siblings of a family with similar clinical phenotype. Diagnosis was made on clinico-radiological grounds followed by confirmation of xanthomata in histopathological examination. This case presentation widens the clinical and radiological spectrum (MRI brain and spine) of CTX and will be discussing in-detail about the differential diagnosis. This report highlights the importance of early diagnosis of a rare inherited treatable metabolic disorder so as to prevent the lethal complications.

Introduction

Cerebrotendinous Xanthomatosis (CTX) is a rare, autosomal recessively inherited disorder of bile acid biosynthesis due to mutation of hepatic mitochondrial enzyme CYP27A1gene, coding for a sterol 27-hydroxylase which normally catalyzes the oxidation of cholesterol to bile acids, on chromosome 2q33-qter, leading to increased deposition of cholesterol and cholestanol in multiple tissues

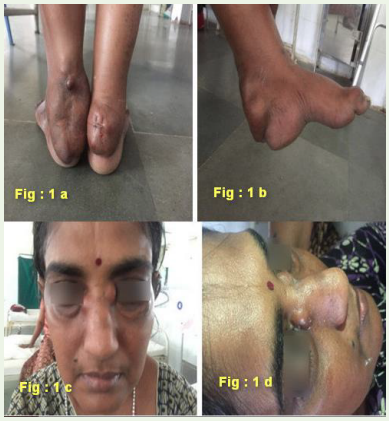

Figure 1: a-d Case 1- showing bilateral xanthomas in achielles tendons and around nose bridge with pes-cavus.

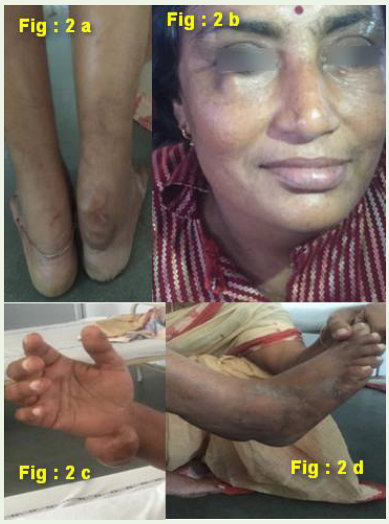

Figure 2: a-d Case 2 -showing xanthomas over Achilles tendons, hands and lower-eyelids.

namely central and peripheral nervous system, soft tissues, lens of the eyes, cardiovascular system, lungs, liver and kidneys [1]. Clinically characterized by progressive dementia, ataxia, spasticity, peripheral neuropathy, accompanied by tendon xanthomas, pre-senile cataracts, premature atherosclerosis and pulmonary dysfunction [2,3]. Early diagnosis is very important, as it is treatable and sometimes reversible. Although reported from many parts of the world, reports from India are rare. We are reporting two cases of CTX.

Case 1 (Index Case)

A 47 year old lady, fourth of five siblings born of consanguinous marriage, suffering from 9 year history of chronic progressive unsteadiness of gait while passing through the narrow passages and was swaying to either side while walking and it did not vary with darkness. She was dull, apathetic, a motivational and withdrawn for 8 years with occasional suicidal thoughts. She was unable to cope up with peers and her scholastic performance was poor. History of tightness and stiffness of the lower limbs were present. History of chronic diarrhoea since 8 years of age, not responding to the usual probiotics. Underwent cataract extraction with lense implantation at 17 years of age. Since 27 years of age noticed multiple swellings started on the left ankle followed by Right Ankle, eyes and nose. Patient`s younger sister was suffering from similar illness.

She was seen by Paediatrician at 3 years of age for delayed motor skills and reassured. At seventeen years of age, bilateral cataract surgery was done by an ophthalmologist. At 40 years of age, left ankle swelling was excised by a General Surgeon which recurred. She had been using homeopathy, ayurveda drugs for 30 years.

On general examination she was short statured (143 cms), Body Mass Index (BMI) of 24.94 with bilateral pescavus with hammer toes, multiple globular swellings over the sides of the bridge of the nose and bilateral Achilles tendons (Figures 1A-1D and Figures 2A-2D). Skin examination showed planar xanthoma.

On neurological examination she was conscious, disoriented to time and place and familiar relatives with scoring of 12/28 on Mini Mental Status Examination (MMSE-Folstein) - suggestive of severe dementia. Bilateral pseudophakia, with amyotrophy of bilateral hands with clawing of fingers, minimal spasticity of all four limbs, with distal weakness of hands and feet. She had brisk tendon jerks with bilateral Babinsky`s. Gait cycle showed wide based stance associated with swaying and dragging of feet. Allied reflexes like Hoffman,

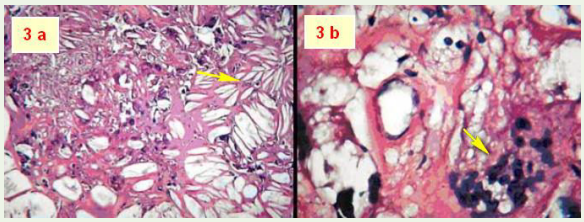

Figure 3: a-b tissue biopsy of xanthomata showing cholesterol clefts (arrow, 3a) and foamy macrophages with multinucleated giant cells (H&E 400X).

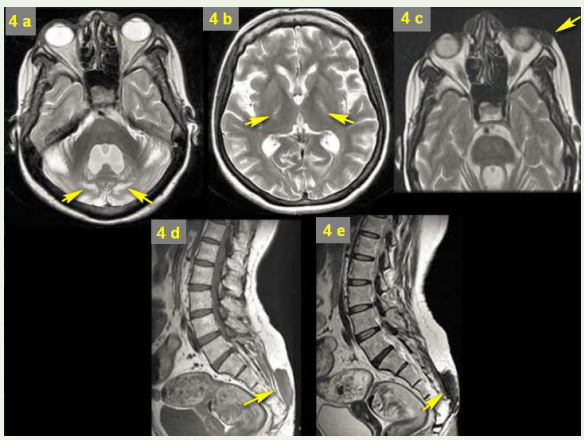

Figure 4: a-c axial T2 w MRI sequence showing hyper intensity of dentate nuclei (arrow 4a), pyramidal tract (arrow head 4b), right eyelid xanthoma (arrow head, 4c), **d-e** sagittal MRI Lumbosacral spine showing gluteal xanthomata (arrow head).

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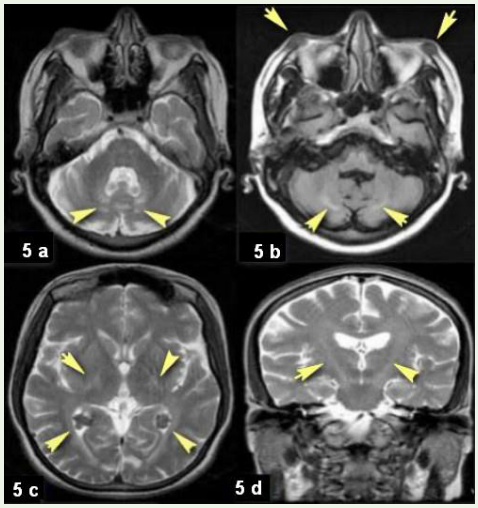

Figure 5: a-b axial T2wMRI and FLARI sequence of Brain of Case 2 showing hyperintensity of dentate nuclei with foliar prominence of cerebellum (arrow head), c- axial T2 wMRI of Brain showing choroid plexus xanthogranuloma (arrow head), **d**-coronal T2 wMRI of Brian showing pyramidal tract hyperintensity (arrow head).

Wartenberg`s were present. Primitive glabellar reflex was present suggestive of neurodegeneration. Significant cerebellar damage was evident through bilateral impaired finger nose ataxia, intentional and kinetic tremors of the hands, Rebound phenomena of the hands, stance ataxia, and severe Gait ataxia. Romberg`s test was positive, vibration sense lost below knee joint in both lower limbs suggestive of large fibre peripheral neuropathy.

Case 2

Her sibling of age 49 years, had the almost similar clinical phenotype with predominant appendicular ataxia, dementia, peripheral neuropathy with spasticity, juvenile cataracts except diarrhoea. She had osteoporosis induced pathological fractures and hypothyroidism with normal blood cholesterol in addition.

Laboratory evaluation in case1 showed hypercholesterolemia (220 mg/dl) with hyper triglyceridemia (369 mg/dl) with LDL: HDL of 3.1 while there was normal cholesterol and elevated TSH of 6.25 micro/ml suggestive of hypothyroidism in case 2. Cardiac screening was normal in both cases.

Histopathology of the tendon swellings from right ankle under haematoxylin and eosin revealed disruption of fibrous collagenous bands of the tendon by masses of Xanthomatous cells containing foamy cytoplasm amassed around cholesterol clefts and multinucleated giant cells, confirming the Xanthomatous tissue (Figures 3A-3B).

Imaging Findings

MRI Brain in the two cases revealed symmetrical T2 and FLAIR hyperintensities in bilateral dentate nuclei of cerebellum with foliar prominence with dilation of fourth ventricle suggesting cerebellar atrophy. Bilateral pyramidal tracts were hyperintense along the posterior limb of internal capsule and crus cerebri on T2 and FLAIR sequences (Figures 4A-4D and Figures 5A-5D). In Case 2 it additionally revealed T2 hypointense lesions in the choroid plexus of bilateral trigone of lateral ventricles suggestive of "choroid plexus xanthogranulomas" (Figure 5C). Careful soft tissue examination showed xanthomas of bilateral lower eyelids in case 2 and left lower lid in index case (Figures 4C and 5B). MRI spine showed normal spinal cord with right gluteal xanthomas which were T1 and T2 hypointense in Case1 (Figures 5D-5E).

MRI of ankles showed bulky achilles tendons with convex anterior margin, well defined heterogenous (iso to hypointense on T1, T2 and STIR relative to adjacent tendons) signal intensity lesion in the distal part of achilles tendon suggestive of Achilles tendon Xanthoma (Figures 6A-6E).

Discussion

Earliest reports of CTX was made by Bogaert's in 1937 followed by few hundred cases worldwide [4,5]. There are no consensus data on the prevalence of CTX, the estimated rate being <5/100000 worldwide. Most patients were traced to Israel, Netherlands, and USA. From India, Sodhi et al. documented the first case of CTX in 1973 [6]. Subsequently by Nair et al. from Trivandrum [7].

CTX can present to different specialists because of its multisystem involvement. It may manifest in neonates and in early childhood with chronic diarrhea, congenital or juvenile cataract, delayed developmental milestones, mental retardation and occasionally, neonatal cholestatic jaundice. The typical triad of neurological dysfunction, tendon xanthoma, and early onset cataract is the clinical hallmark. This is often not found on first contact with specialist. Bordia and Saifee from India reported oro-mandibular dyskinesia as the presenting feature of CTX which was seen at first by dentist [8]. CTX shares presence of xanthoma and premature atherosclerosis with other lipid storage disorders including familial hyper cholesterolemia and sitosterolemia. Progressive neurological dysfunction and early cataract are seen in CTX only.

The presented cases highlighted the classical manifestations of CTX in the form of progressive dementia, pyramidal, cerebellar, peripheral neuropathy in association with bilateral cataracts, tendon and eyelid xanthomas on a background of chronic diarrohea. Case

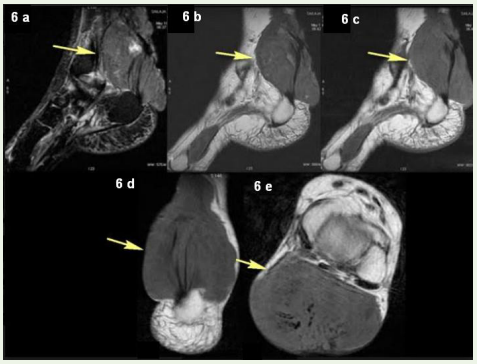

Figure 6: a-e MRI of ankle of case 1 showing iso to hypointense on T1, T2 and STIR relative to adjacent tendons showing xanthomatosis (arrow heads).

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Table 1: Differential diagnosis based on clinical features.

Clinical features	Sitasterolemia	Smith LemliOpitz syndrome	Familial Hyper cholesterolemia	MSS Marnesco Sjogrensyn	CTX
Inheritance	AR	AR	AD	AR	AR
Bilateral Cataract	Absent	Present	Absent	Present	Present
Xanthomas	Present	Present	Present	Absent	Present
Chronic Intractable Diarrhoea	Absent	Absent	Absent	Present	Present
Neurological manifestations	No	Deafness Dysarthria Hypotonia	No	Cerebral Cerebellar atrophy	Cerebellar ataxia Dementia Pyramidal Extrapyramidal

2, also had hypothyroidism, osteoporosis induced pathological fractures. The clinical syndrome may include other neurological features like fronto-temporal dementia [9,10], extra pyramidal symptoms, including dystonia and oromandibular dyskinesia [8], early-onset Parkinson disease [11], seizures [12], muscular symptoms like myopathic facies [13].

According to the clinical suspicion index of Mignarri et al. for CTX, where our both cases had all the four clinical features evolved in the same order as described like diarrohea, presenile cataracts, xanthomas and neurological abnormalities [14].

Xanthomas are rarely seen before 20 years of age and usually develop over Achilles tendons, patella, elbow, hands and neck regions. They have also been reported on the parenchyma of the lungs and brain, as well as in the bones. Our cases had xanthomas onset after 20 years of age, involving the achilles tendons, eyelids, nasal bridge, around the wrist and gluteal regions.

Soffer and colleagues [15] demonstrated that the parenchymal destruction in the brain starts in the white matter with cholestanol cumulation and progresses in a centrifugal manner with axonal spheroids being more marked in the brainstem with decreasing order of severity in the centrum semiovale. The presenile cataracts of CTX contain high cholestanol compared to the cholesterol of senile cataracts.

Earliest and most important abnormalities are noted in the cerebellum with high signal of deep gray nuclei namely dentate nuclei with occsaional hypointensity. Sometimes white matter lesions are surrounded by rim of hypointensity in T2 weighted images suggestive of macroscopic xanthomata, calcium or hemosiderin deposits. Neuro-imaging modalities demonstrate diffuse atrophy of the brain, as well as focal lesions (including demyelinating lesions and, rarely, xanthomata) in the cerebellum, basal ganglia, and cerebrum. CT scan is less sensitive but MRI abnormalities are obvious. Typical patterns on MRI brain include bilateral lesions consistent with a metabolic abnormality. Destefano et al. had reported T2 hyperintensity of the dentate nuclei as an earliest and characteristic finding of CTX in their 79% of patients [16]. T2 abnormalities are also found in the globus pallidus, substantia nigra, and inferior olives with extension into the surrounding white matter with sparing of the U fibers and the corpus callosum in later years of the disease. Hence CTX should be considered in the differential diagnosis of leukodystrophies [17].

Focal lesions in the brain involving the corona radiata, centrum semiovale, globus palldum [18,19], and posterolateral columns of spinal cord [19] are described and on the other hand brainstem, corpus callosum [19] and atrophy of spinal cord [20], have been reported.

Choroid plexus xanthogranulomas are benign tumors composed of xanthoma cells (macrophages), cholesterol clefts, chronic inflammatory cellular reaction, and hemosiderin. At autopsy series they have been found incidentally in 1.6-7% of cases [21]. These lesions are most commonly seen bilaterally in the lateral ventricles; they are asymptomatic because they are too small to obstruct the ventricles. However, those occurring in the third ventricle are more likely to present with non-communicating hydrocephalus. Hypointensity on T2 weighted MR sequence is classical of xanthomatous tissue. Similar demonstration of bilateral choroid plexus xanthogranuloma in a patient with CTX was reported by Fiorelli et al. [22].

Magnetic resonance spectroscopy reveals diffuse mitochondrial dysfunction and axonal damage, with large amounts of lactate and decreased *N* -acetylaspartate in the periventricular white matter and cerebellar hemispheres [16]. Similar findings can as well be reflected in the affected xathomatous tissues.

Isolated spinal cord white matter disease has been described [20-23]. MRI may reveal increased intensity in the lateral and dorsal columns, even in mainly cerebral forms of the disease [16]. Magnetization transfer imaging has been found to be a reliable quantitative indicator of the extent of damage in the brain parenchyma [23]. MRI can also be used to evaluate possible tendon xanthomata outside the central nervous system; enlargement of the tendons and xanthomas of eyelids as evident in our case.

Treatment of this disease includes the combination of CDCA (300 mg/day) and HMG Co A inhibitor (Simvastatin/Pravastatin 10 mg/day) is more effective in reducing cholestanol levels and normalizing LDL cholesterol [24,25], LDL pheresis, and dietary modifications. The results of treatment are variable, there was either arrest of the disease progression or partial improvement of clinical, biochemical, and MRI abnormalities. Genetic analysis is important in identifying the carriers of the disease. Early institution of CDCA therapy can prevent development of CTX phenotype. It improves bile acid metabolism and decreases cholestanol levels. The drug CDCA is not available in India and is very expensive.

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Conclusion

Being a multisystemic disease, high index of suspicion is required among the specialities to diagnose CTX whenever patients present with mental retardation, presenile cataract, intractable diarrhoea with or without neurological involvement. Imaging abnomralities are numerous and almost speculate the pathology of the underlying disease. After significant disease progression, treatment does not readily reverse neurological deficits that have already occurred.

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