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Case Report

Cerebrotendinous xanthomatosis; a genetic condition: Clinical profile of three patients from a rural Indian family and review of literature

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ABSTRACT

Introduction: Cerebrotendinous xanthomatosis is a rare lipid storage disease characterized by infantile onset diarrhea, cataract, tendon xanthomas, and progressive neurologic dysfunction. Cerebrotendinous xanthomatosis is exceptionally rare in Indian population with only few case reports till now.

Case report: An 18-year-old male presented to orthopedic outpatients clinic with complaints of insidious onset swelling of both achilles over last 3 years, with history of learning and visual difficulties. On examination, there were firm nontender swellings along the course of both tendoachillis. Plantar response was extensor and Romberg test was positive with eyes closed. Cranial MRI showed diffuse cerebral and cerebellar atrophy. Family history showed history of diarrhea, mental retardation, and visual difficulties in his two younger siblings. They were also called upon and evaluated clinically. All three were diagnosed as having cerebrotendinous xanthomatosis based on clinical and radiological features.

Conclusion: Cerebrotendinous xanthomatosis is a progressive and preventable disorder and it benefits from therapy, so early diagnosis is mandatory to prevent significant morbidity and mortality associated with this disease.

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1. Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive, metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurologic abnormalities. It is extremely rare in Indian population with

limited Indian data.^{1–7} Untreated CTX follows a progressive course. Four clinical criteria are used in diagnosis. The criteria include intractable diarrhea, presenile cataract, tendinous xanthomas, and neurologic abnormalities. The clinical features usually manifest in that order; however, atypical presentations have been reported and the disease spectrum is variable even within families. Early diagnosis is

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important as it is a treatable disorder and the progress of the disease can be prevented with timely intervention. We present clinical features of three patients with CTX from the same family.

2. Case report with family profile

An 18-year-old male presented to OPD with slow and progressive enlargement of tendinous nodule on posterior aspect of both ankles for last 3 years. The disease had progressively worsened in last 3 months with difficulty in walking. The patient was short stature with elongated face and slightly opened mouth, having learning difficulties and blurred vision. Physical examination did not reveal nodule or mass anywhere else in the body. The ophthalmic examination revealed bilateral dense cataract with severely diminished vision (6/60 in both eye), and fundus was hazy due to presenile posterior polar cataract with pale optic disc and dull macular reflex. Neurological examination revealed plantar extensor response and positive Romberg test with eye closed. The patient was mentally subnormal (intelligence quotient 55) and nerve conduction study showed mild axonal neuropathy in both upper and lower limbs. MRI examination showed cerebral and cerebellar atrophy. The patient's serum cholesterol was slightly raised and serum uric acid level was normal and he was not taking any sort of medication. The blood cholestanol level could not be ascertained due to non-availability of the test. There was no history of antecedent trauma. Karyotyping study of his parents and himself was done to rule out other genetic causes of mental retardation and was found normal. He was born of non-consanguineous marriage and the delivery was full term vaginal without any neonatal hypoxia and jaundice; however, parity was of higher order. His two elder siblings were normal while two younger siblings were mentally subnormal. There was history of infantile onset intractable diarrhea in younger two siblings and visual difficulty in immediate younger male sibling. The physical examination showed short stature and severe mental retardation in both younger siblings. Male sibling was having severely diminished vision (finger counting at a distance of 1 m in right eye and 6/60 in left eye) and dense presenile cortical cataract in both eyes. Fundus examination was not possible due to dense cataract. Visual acuity and fundus examination were normal in female sibling. Neurological examination showed extensor plantar response but tone and deep tendon reflexes were normal. Musculoskeletal examination did not show any evidence of xanthomatosis. ECG and echocardiogram of all three patients were normal. Bilateral xanthomas of achilles tendon were excised and reconstructed with fascia lata graft. The excised specimens were sent for histological confirmation. Based on typical clinical profile of the patients, diagnosis of CTX was made and the patients were put on chenodeoxycholic acid (CDCA) in a dose of 250 mg thrice a day, after which two siblings showed relief from intractable diarrhea but no relief in mental status. For the management of cataract, the patient and his younger siblings were referred to ophthalmic surgeon (Figs. 1–4).

Fig. 1 – Clinical appearance of bilateral tendoachillis xanthomas.

Fig. 2 – Excised specimen of tendoachillis xanthomas showing pale, waxy cylindrical grayish white soft tissue mass.

Fig. 3 – MRI brain showing cerebral and cerebellar atrophy.

Fig. 4 – Ocular findings in CTX patients; showing bilateral posterior polar cataract with hazy fundus in first patient and bilateral dense cortical cataract with hazy fundus in second patient.

3. Discussion

We made the diagnosis of CTX on the basis of clinical profile of these three patients from the same family. Approximately 300 cases of CTX have been reported worldwide, but probably the incidence is underestimated.⁸ The disease was first described in 1937 by Van Bogaert.⁹ In 1968, Menke et al.¹⁰ described the accumulation of cholestanol, the primary metabolite found in elevated concentration in CTX (Table 1).

CTX is a rare genetic metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurologic abnormalities. In patients with CTX, primary enzymatic defect is in the activity of the hepatic mitochondrial enzyme sterol 27-hydroxylase, a key enzyme in the bile acid synthesis.¹¹ Therefore, synthesis of cholic acid is reduced, and almost no CDCA is produced. The negative feedback of CDCA on the rate-limiting enzyme in bile acid biosynthesis, 7 alpha-hydroxylase, decreases and by way of a side pathway, an excessive amount of cholestanol that accumulates in many tissues is produced. By 24- and 25-hydroxylase pathways, bile alcohols are produced in patients with CTX.¹² Biochemical diagnosis is made by determining the excessive urinary excretion of bile alcohols and the serum cholestanol level.

Clinical presentation of CTX varies considerably but no genotype-phenotype correlation has been established. CTX is characterized by infantile onset diarrhea, childhood onset cataract, adolescent to young adult onset tendon xanthomas, and adult onset progressive neurologic function. Chronic diarrhea from infancy may be the earliest clinical manifestation of CTX.^{13,14} In approximately 75% of affected individuals, cataracts are the first finding, often appearing in first decade of life. The appearance can include irregular cortical opacities, anterior polar cataracts, and dense posterior subcapsular cataract.¹⁵ Other ocular finding may include palpebral xanthelasmas, optic nerve atrophy, and proptosis. Xanthomas occur in the second or third decade and they usually involve the achilles tendon, the extensor tendon of elbow and hand, and the patellar tendon. Xanthomas have been reported in lung, bones, and central nervous system. Achilles tendon

xanthomas are characteristic of the disorder and clinically resemble those seen in familial hypercholesterolemia or hyperlipoproteinemia but biochemical analysis reveals that they contain high amounts of cholestanol and little cholesterol.⁴ Neurologic symptoms and signs include cerebellar and pyramidal dysfunction, dementia, epilepsy, Parkinsonism, polyneuropathy, and mental retardation. CTX has been associated with marked cardiovascular findings including premature atherosclerosis, coronary and carotid vascular disease,^{16,17} and atrial septal hypertrophy.¹⁸ Granulomatous bone lesions typically in the femur and lumbar vertebrae, osteopenia, osteoporosis, and pathological fracture have been described in CTX. Hypothyroidism has occasionally been reported. Early onset cataract, osteopenia with fractures and loss of teeth, atherosclerosis, neurologic impairment with dementia, and/or Parkinsonism associated with the characteristic facies suggest a generalized premature aging process.¹⁸

Investigation shows elevated serum cholestanol level. Serum cholesterol and triglyceride levels are normal. Neuroimaging shows changes of cerebral and cerebellar atrophy on CT and MRI. Typical pattern on MRI includes bilateral lesions consistent with a metabolic abnormality. T2 hyperintensity of the dentate nuclei is characteristic of CTX.

Clinically, CTX may resemble the Marinesco-Sjogren syndrome, an autosomal recessive disorder, which is characterized by the triad of cerebellar ataxia, congenital cataract, and mental retardation.¹⁹ The presence of tendon xanthomas, diarrhea, increased serum cholestanol, and urinary bile alcohol helps in differentiating CTX from this condition. This differentiation is important as latter is a treatable disorder. Other differential diagnosis for CTX includes hypercholesterolemia, leukodystrophies, sitosterolemia, and Smith Lemli Opitz syndrome.

The treatment of choice in CTX is CDCA replacement therapy. It was first reported by Berginer et al.²⁰ If hypercholesterolemia is not controlled with CDCA treatment alone, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors (i.e., statins) may be added. HMG-CoA reductase inhibitors have well-established efficacy and safety in patients with hypercholesterolemia and have also been used alone and in combination with CDCA to treat CTX.

Table 1 – Clinical profile of three patients with cerebrotendinous xanthomatosis from same family.

Patient number	Parity of patient	Age	Sex	Weight (kg)	Height (cm)	History				Examination			
						Intractable diarrhea	Visual difficulty	Neurological symptoms	Xanthomatosis	Ophthalmic examination	CNS examination	Musculoskeletal examination	Cardiovascular examination
1	5	18	Male	35	147	Absent	+++	++	Bilateral achilles	Presenile posterior polar cataract in both eyes	Normal tone Plantar extensor Romberg + Deep tendon reflex normal	Pes planus	ECG normal Echocardiogram normal
2	6	14	Male	20	127	Present	+++	+++	–	Dense presenile cortical cataract	Normal tone Plantar extensor Deep tendon reflex normal	Normal	ECG normal Echocardiogram normal
3	7	11	Female	14	97.5	Present	–	+++	–	No lenticular opacity	Normal tone Plantar extensor Deep tendon reflex normal	Normal	ECG normal Echocardiogram normal

In our case, younger three of the five siblings had features of CTX. All three patients were having mental retardation. First patient had bilateral tendoachillis xanthomas along with presenile cataract. He was also having cerebellar ataxia, positive Romberg, and polyneuropathy. His younger male sibling was having history of infantile onset diarrhea along with presenile cataract while female sibling was having history of frequent loose stools but no visual abnormalities.

Unfortunately, as in our case, the disease is usually not diagnosed on time and all these three patients kept on being treated symptomatically for mental retardation, diarrhea, and visual difficulties by various practitioners with poor results. It was bilateral xanthomatosis that brought the patient to us and after thorough history and proper examination along with systemic review of literature, we could establish the diagnosis of CTX. Therefore, early diagnosis of this rare metabolic disease is necessary and CTX should be considered in differential diagnosis of every patient with intellectual impairment, spastic, ataxic signs, juvenile cataract, infantile onset diarrhea, and tendon xanthomas and MRI imaging should be done as soon as possible. By early diagnosis and proper treatment with CDCA, potential systemic complications of this disease can be prevented.

Conflicts of interest

The authors have none to declare.

REFERENCES

- Chatterjee G, Chakraborty I, Das TK, Dutta C. Cerebrotendinous xanthomatosis in a family. *Indian J Dermatol*. 1999;44:153–156.
- Bordia S, Saifee AA. Cerebrotendinous xanthomatosis with oromandibular dyskinesia. *Neurol India*. 2003;51:556–558.
- Gaikwad SB, Garg A, Mishra NK, Gupta V, Srivastava A, Sarkar C. Cerebrotendinous xanthomatosis: neuroimaging findings in two siblings from an Indian family. *Neurol India*. 2003;51:401–403.
- Muhammad K, Nandkumar G, Saritha S. Cerebrotendinous xanthomatosis: need for early diagnosis. *Indian J Dermatol Venereol Leprol*. 2006;72(5):354–355.
- Jha S, Khateeb M, Sonker K. Cerebrotendinous xanthomatosis, early diagnosis mandatory: report of a case from north India. *Neurol Asia*. 2008;13:125–128.
- Karandikar AA, Pushparajan S, Unni MN, Srinivas R. Case report cerebrotendinous xanthomatosis. *Indian J Radiol Imaging*. 2009;19(4):314–317.
- Mukherjee AA, Chawla BP, Rath SS, Puthran RS. Cerebrotendinous xanthomatosis: a treatable cause of metabolic ataxia. *JAPI*. 2007;55:655–657.
- Gonzalez-Cuyar LF, Morrison AL, Perry G, DeJong JL, Smith MA, Castellani RJ. Cerebrotendinous xanthomatosis: a critical update. *Future Neurol*. 2008;3:491–501.
- Bogaert L, Scherer H, Epstein E. *Une forme cerebrale de la cholesterinose generalise*. Paris, France: Masson et Cie; 1937.
- Menkes JH, Schimschock JR, Swanson PD. CTX: the storage of cholesterol within the nervous system. *Arch Neurol*. 1968;19:47–53.
- Oftebro H, Björkhem I, Stormer FC, Pedersen JL. Cerebrotendinous xanthomatosis: defective liver mitochondrial hydroxylation of chenodeoxycholic acid precursors. *J Lipid Res*. 1981;22:632–640.
- Björkhem I, Boberg KM. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Scriver C, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Basis of Inherited Disease* 7th ed. New York, NY: McGraw-Hill; 1995:2273–2299.
- Cruysberg JR. Cerebrotendinous xanthomatosis: juvenile cataract and chronic diarrhea before the onset of neurologic disease. *Arch Neurol*. 2002;59:1975.
- Cruysberg JR, Wevers RA, Tolboom JJ. Juvenile cataract associated with chronic diarrhea in pediatric cerebrotendinous xanthomatosis. *Am J Ophthalmol*. 1991;112:606–607.
- Cruysberg JR, Wevers RA, van Engelen BG, Pinckers A, van Spreken A, Tolboom JJ. Ocular and systemic manifestations of cerebrotendinous xanthomatosis. *Am J Ophthalmol*. 1995;120:597–604.
- Schimschock JR, Alvord EC, Swanson PD. Cerebrotendinous xanthomatosis. Clinical and pathological studies. *Arch Neurol*. 1968;18:688–698.
- Frih-Ayed M, Boughammoura-Bouatay A, Ben Hamda K, Chebel S, Ben Farhat M. Hypertrophy of the atrial septum in the cerebrotendinous xanthomatosis. *Rev Med Interne*. 2005;26:992–993.
- Dotti MT, Mondillo S, Plewnia K, Agricola E, Federico A. Cerebrotendinous xanthomatosis: evidence of lipomatous hypertrophy of the atrial septum. *J Neurol*. 1998;245:723–726.
- Siebner HR, Berndt S, Conrad B. Cerebrotendinous xanthomatosis without tendon xanthomas mimicking Marinesco-Sjögren syndrome: a case report. *J Neurol Neurosurg Psychiatry*. 1996;60:582–585.
- Berginer VM, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. *N Engl J Med*. 1984;311:1649–1652.