

Cerebrotendinous Xanthomatosis: Report of two cases and a novel genetic mutation in an Indian patient

Bhupender K Bajaj, Anand Singh, Kuljeet S Anand, Jyoti Garg

Department of Neurology, PGIMER and Dr. RML Hospital, New Delhi, India

ABSTRACT

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessive disorder of bile acid metabolism manifesting typically with the triad of neurological dysfunction, tendon xanthoma, and early onset cataract. The diagnosis is often missed and delayed as the patients do not manifest all the classical features. Early recognition and initiation of chenodeoxycholic acid therapy with Hydroxymethylglutaryl Coenzyme-A (HMG-Co-A) inhibitors is critical to prevent irreversible neurological damage and permanently disabled existence. We report about two patients, both of whom remained undiagnosed for more than 20 years. Genetic analysis in one of the patients revealed a novel genetic mutation in one of the homologous genes. The patient was found to have heterozygous mutation of CTX gene with a novel mutation in exon 1 of CYP27A1 gene.

Key words: Ataxia, cataract, cerebrotendinous xanthomatosis, cerebellar hyperintensities, genetic mutation, quadriparesis

Introduction

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessive inborn error of lipid metabolism manifesting characteristically with neurological dysfunction, juvenile cataract and tendinous xanthoma. It is a treatable disorder which often remains unrecognized till late in its course due to its' protean manifestations and lack of suspicion on part of treating specialists. An estimated prevalence of 1 in 50,000 to 70,000 population has been mentioned in some of the published studies.^[1,2] If similar prevalence is presumed for Indian population, one would expect to have 12000 to 20000 such patients in India. In practice, it appears that we are not diagnosing CTX as often. This could be due to lower prevalence of the CTX gene in Indian population or under-recognition

of it. The disorder has variable manifestations leading to misdiagnosis particularly early in the course when there are no xanthomas and the clinical presentation appears similar to other childhood and young adult onset neurological diseases. We report here two cases of CTX who had different presentations and remained undiagnosed till they had significant permanent physical impairment. One of the patients, in whom genetic analysis was done, had a novel mutation of CTX gene.

Case Reports

Case 1

A 50-year-old commerce graduate with degree in law presented to us with insidious onset gradually progressive spastic diplegia for 20 years followed later by gradually progressive bladder dysfunction, poor scholastic performance, and a single seizure. He was born to non-consanguineous parents and had unremarkable early psychomotor development. Pedigree analysis revealed absence of any family history in previous two generations. On examination, patient had thoracic kyphosis with contractures at hip, knee, and ankle joints. He had firm, non-tender swellings over ankles, patella,

Access this article online

Quick Response Code:



Website:
www.ruralneuropractice.com

DOI:
10.4103/0976-3147.116420

Address for correspondence:

Dr. Bhupender Kumar Bajaj, Department of Neurology, PGIMER and Dr. RML Hospital, New Delhi, India. E-mail: docbajaj@yahoo.co.in

and elbows bilaterally [Figure 1]. Detailed higher mental function assessment revealed impairment of attention, new learning and visual memory with normal language functions. His speech was slow and slurred but could be comprehended with little difficulty. All cranial nerve functions were intact. The patient had severe spasticity in both lower limbs with brisk deep tendon reflexes in both the upper and the lower limbs, extensor plantar responses, and normal sensory examination.

Blood investigations revealed a normal complete hemogram (including hemoglobin, total leukocyte count, differential leukocyte count), liver and kidney function tests, serum electrolytes and, triglyceride and cholesterol levels. X-rays of ankle, knee, and elbow showed homogenous soft tissue swelling. MRI brain showed T2-weighted hyperintensities in dentate nucleus regions bilaterally and generalized cerebral and cerebellar atrophy [Figure 2]. Plasma cholestanol levels were found to be raised [16.8µg/ml; normal laboratory reference range: 4.2 ± 1.2 (S.D)] suggesting cerebrotendinous xanthomatosis. The genetic analysis of CYP27A1 gene of the patient was carried out by the method of Polymerase Chain Reaction and sequencing of both the DNA strands was done. The analysis revealed heterozygous mutation in exon 6 with substitution of cytosine by thymine at 1151 position (c. 1151C > Tp. P384L) and a novel mutation in exon 1 of CYP 27 gene with substitution of thymine by cytosine at nucleotide position 2 of the gene (c. 2T > Cp.M1T). The mutation in exon 6 is already described as disease causing while the mutation in exon 1 is previously unreported as per the current Human Gene Mutation Database. The mutation causes loss of a highly conserved start codon and likely results in loss of functional protein. The patient is receiving atorvastatin besides physical therapy and chenodeoxycholic acid (CDCA) is being arranged as it is not marketed in India.

Case 2

The second case was of a 28-year-old male who was born of a non-consanguineous marriage, had delayed psychomotor milestones with mental retardation, congenital cataract, and recurrent episodes of diarrhea since early childhood. He had history of progressive spastic diplegia, tremulousness in both upper limbs and scanning speech. The patient had impaired attention, vigilance, comprehension, and new learning ability. Pan-sensory impairment was noted below knee with impaired limb coordination in upper limbs.

Patient's skin biopsy of swelling over Achilles confirmed xanthoma [Figure 3]. MRI brain showed altered signals in bilateral cerebral peduncles, ventral pons, both the



Figure 1: Photograph showing xanthomatous swelling over Achilles and elbows (marked with arrows)

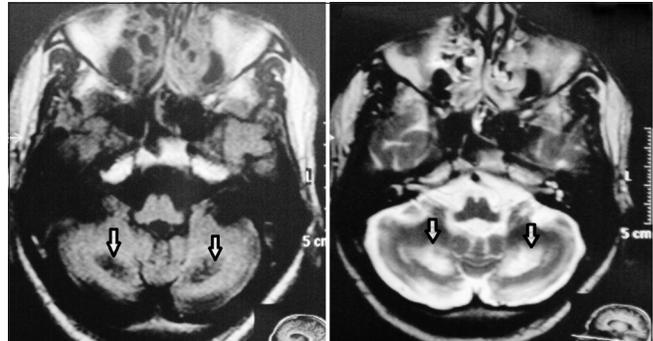


Figure 2: MRI brain showing T1W hypointensities and T2W hyperintensities in bilateral cerebellar hemispheres in dentate nuclei region

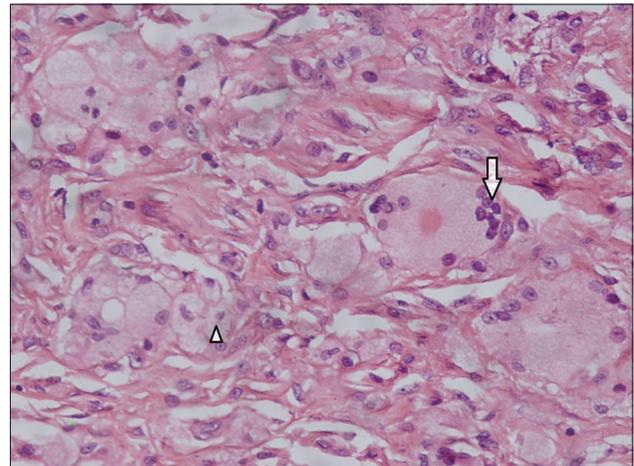


Figure 3: H & E, stain of xanthoma over Achilles tendon region showing foam cells (arrow head) and multinucleate giant cell (arrow)

middle cerebellar peduncles and medullary pyramids. Based on the clinical, radiological, and biopsy findings of the Achilles tendon swelling, diagnosis of CTX was confirmed.

Review of literature

Cerebrotendinous xanthomatosis is an autosomal recessive disorder of lipid metabolism resulting from homozygous or compound heterozygous mutations in CYP27A1 gene on chromosome 2q. The mutation results in deficient sterol 27 hydroxylase activity with resultant impaired formation

of CDCA and accumulation of metabolic intermediary, cholestanol [Figure 4]. The cholestanol starts depositing in lipophilic tissues including brain, spinal cord, lens of eyes, and tendons. Bile acid becomes deficient in CDCA and has higher cholestanol contents. The patients also develop premature atherosclerosis secondary to cholesterol and cholestanol deposits in the vessel wall. The first description of the clinical features of the disease is attributed to Van Bogaert. Cholestanol deposition in tissues was elucidated in 1971 by Menkes *et al.*^[3] The disease is traditionally believed to be a rare disorder in most ethnic groups. There are more than 50 known mutation of CYP27A1 gene in literature.^[4] Certain ethnic groups such as Sephardims of Moroccan origin have been reported to have high mutant gene carrier frequency of 1:108.^[5] Mathew *et al.* noted one carrier of CYP27 gene mutation R362C among 115 control white population.^[1] They estimated that prevalence of CTX gene mutation R362C among the white ethnic population to be 1.9 per 10⁵. There are many more mutations in CYP27 gene besides the R362C. It is estimated that the prevalence of CTX is 3-5 per 10⁵ population in whites. There is no published report of genetic analysis in Indian patients. The cases presented here remained undiagnosed for more than 20 years after the clinical manifestations despite having been examined by various specialists. If the prevalence of gene mutation in Indian population is similar to the whites, assuming 1.2 billion Indian populations, the estimated number of CTX cases in India should be around twenty thousands. Our case reports reinforce the possibility of misdiagnosis or underdiagnosis of the condition in Indian population. We came across nine reports of cerebrotendinous xanthomatosis in Indian literature.^[6-14] Ours is the first report of genetic mutation analysis reported in an Indian patient.

Cerebrotendinous Xanthomatosis can present to different specialists because of its multisystem involvement. It may manifest in neonatal and early childhood period

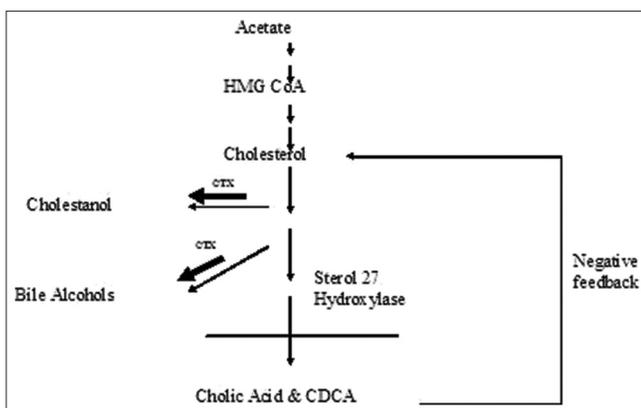


Figure 4: Schematic representation of chenodeoxycholic acid synthesis from cholesterol

with chronic diarrhea, congenital or juvenile cataract, delayed developmental milestones, mental retardation and occasionally, neonatal cholestatic jaundice. Tendon xanthomas and neuropsychiatric symptoms often manifest only in second and third decades. Adult patients may manifest with spastic quadriplegia, diplegia, paraparesis, bulbar paresis, cerebellar ataxia, extrapyramidal symptoms, progressive cognitive deterioration, and peripheral neuropathy. The patients may have pes cavus, osteoporosis, and bone fractures. There is great variability in the age of manifestation of all these features. Classical clinical triad is often not found on first contact with specialist. Bordia and Saifee from India reported oromandibular dyskinesia as the presenting feature of CTX.^[9] Their patient had recurrent temporomandibular dislocation and was first seen by dentist. High index of suspicion alone can help detect the condition in early stages and prevent subsequent neurological complications and permanent disability. Cerebrotendinous xanthomatosis shares presence of xanthoma and premature atherosclerosis with other lipid storage disorders including familial hypercholesterolemia and sitosterolemia. Progressive neurological dysfunction and early cataract are seen in cerebrotendinous xanthomatosis only. Both our patients had T2 hyperintensities in cerebellar hemispheres with prominent involvement of dentate nuclei on MRI brain. In addition to cerebellar hyperintensities, CTX patients may have multiple white matter T2 hyperintensities in cerebral hemispheres and, cerebral and cerebellar atrophy. Spinal cord MRI may also show evidence of white matter hyperintensities due to xanthomatous deposition. MRI spine was done in the first patient and did not show any abnormality. Despite significant changes in cerebellum on MRI, significant ataxia was not noted either historically or on examination in our first patient. Biopsy of tendon xanthoma or subcutaneous swellings often reveals foam cells and Touton giant cells.^[6] Spindle-shaped clefts are seen in the xanthomas on hematoxylin and eosin staining and rod shaped collections are seen on electron microscope.

Treatment with CDCA is known to halt progression of disease. Studies have shown that early institution of CDCA therapy can prevent development of CTX phenotype. CDCA improves bile acid metabolism and decreases cholestanol levels. It has been observed that the combination of CDCA and HMG Co A inhibitor Simvastatin is more effective in reducing cholestanol levels and normalizing LDL cholesterol.^[15] The drug, CDCA, is not available in India and is very expensive.

It is imperative to recognize and treat CTX early in course. The diagnosis of CTX should be suspected and

ruled out in all cases of congenital or juvenile cataract, spastic diplegia, paraparesis, quadriparesis or ataxia or combinations of these features particularly on a background of chronic diarrhea even in the absence of tendinous xanthomas, which often do not appear till 2nd decade of life. Raised plasma cholestanol levels are diagnostic of the disease early in course. Genetic testing in presymptomatic family members of affected patients should be done and CDCA therapy instituted to prevent the disease manifestations.

Acknowledgement

Department of Medical Genetics, Sir Ganga Ram Hospital for assistance in getting genetic testing done.

References

- Lorinez MT, Ranier S, Thomas D, Fink JK. Cerebrotendinous xanthomatosis: Possible higher prevalence than previously recognized. *Arch Neurol* 2005;62:1459-63.
- Rafiq M, Sharrack N, Shaw PJ, Hadjivassilou M. A neurological rarity not to be missed: Cerebrotendinous xanthomatosis. *Pract Neurol* 2011;11:296-300.
- Menkes JH, Schimschok JR, Swanson PD. Cerebrotendinous xanthomatosis: The storage of cholestanol within the nervous system. *Arch Neurol* 1968;19:47-53.
- Tian Di, Zaiquiang Z. 2 novel deletions of the sterol 27 hydroxylase gene in a Chinese family with cerebrotendinous xanthomatosis. *BMC Neurol* 2011;11:130.
- Berginer VM, Abeliovich D. Genetics of cerebrotendinous xanthomatosis (CTX): An autosomal recessive trait with high gene frequency in Sephardim of Moroccan origin. *Am J Med Genet* 1981;10:151-7.
- Chatterjee G, Chakroborty I, Das TK, Datta C. Cerebrotendinous xanthomatosis in a family. *Indian J Dermatol* 1999;44:153-6.
- Mukherjee AA, Chawla BP, Rathi SS, Puthran RS. Cerebrotendinous xanthomatosis: A treatable cause of metabolic ataxia. *J Assoc Physicians India* 2007;55:655-7.
- Srinivas BJ, Patnayak R, Rao IS, Prayaga A, Khan AK, Narasimhlu G. Cerebrotendinous xanthomatosis: A case report. *Acta Cytol* 2007;51:654-6.
- Bordia S, Saifee AA. Cerebrotendinous xanthomatosis with oromandibular dyskinesia. *Neurol India* 2003;51:556-8.
- Jha S, Khateeb M, Sonker K. Cerebrotendinous xanthomatosis, early diagnosis mandatory: Report of a case from North India. *Neurology Asia* 2008;13:125-8.
- Kamate M, Chetal V, Hattiholi V. Cerebrotendinous xanthomatosis. *Indian J Pediatr* 2010;77:697-8.
- Gaikwad SB, Garg A, Mishra NK, Gupta V, Srivastava A, Sarkar C. Cerebrotendinous xanthomatosis: Neuroimaging findings of two siblings from an Indian family. *Neurol India* 2003;51:401-3.
- Muhammed K, Nandakumar G, Saritha S. Cerebrotendinous xanthomatosis: Need for early diagnosis. *Indian J Dermatol Venereol Leprol* 2006;72:364-6.
- Karandikar AA, Pushparajan S, Unni MN, Srinivas R. Case report: Cerebrotendinous xanthomatosis. *Indian J Radiol Imaging* 2009;19:314-7.
- Verrips A, Wevers RA, Baziel GM, Engelen V, Keyser A, Wolthers BG, *et al.* Effect of Simvastatin in addition to Chenodeoxycholic acid in patients with cerebrotendinous xanthomatosis. *Metabolism* 1999;48:233-8.

How to cite this article: Bajaj BK, Singh A, Anand KS, Garg J. Cerebrotendinous Xanthomatosis: Report of two cases and a novel genetic mutation in an Indian patient. *J Neurosci Rural Pract* 2013, 4(Suppl 1):s87-90.
Source of Support: Nil. **Conflict of Interest:** None declared.