CEREBROTENDINOUS XANTHOMATOSIS: CASE REPORT ON A RARE GENETIC DISEASE

Goutam Chowdhury[1*] Pradip Kumar Kayasthagir[2] Abhijit Chowdhury[3]

Abstract

Cerebrotendinous Xanthomatosis (CTX) is a rare inborn progressive lipid storage disorder of autosomal recessive inheritance pattern.The multisystem disease causes decreased bile acid synthesis alongside cholesterol and cholestanol deposition in various tissue sites. This case report focuses on describing a middle-aged Bangladeshi male patient presented chiefly with neurological symptoms of CTX who received treatment with Chenodeoxycholic Acid (CDCA).

Key words

Cerebrotendinous Xanthomatosis; CYP27A1; Cholestanol; Chenodeoxycholic Acid.

Introduction

CTX results from the CYP27A1 gene mutation located on the chromosome 2q33-qter causing decreased enzyme mitochondrial sterol 27-hydroxylase[1]. This gene is crucial in cholesterol side chain oxidation during the synthesis of Chenodeoxycholic acid[2]. Mutation in the CYP27A1gene leads to reduced enzyme activity resulting cholestanol deposition in multiple tissues like the brain, lungs and tendons[2]. This syndrome manifests as a triad of early bilateral cataract, tendon xanthomas and neurological anomalies. It may also cause osteoporosis and premature atherosclerosis[3]. CTX initially manifests with non-neurological features and patients later develop adult-onset neurological symptoms like spinocerebellar or spastic ataxia, psychosis, peripheral neuropathy and dementia[1]. Early diagnosis and long-term treatment with CDCA are of utmost importance in preventing various multisystem detrimental sequelae of this debilitating disease[4].

1. Consultant of Radiology & Imaging
Chevron Clinical Lab (PTE) Ltd, Chittagong.
2. Assistant Professor of Neurology
Chittagong Medical College, Chittagong.
3. PhD Research Fellow
Centre for Clinical Epidemiology and
Biostatistics Hunter Medical Research Institute
The University of Newcastle, Australia.

***Correspondence:** **Dr. Goutam Chowdhury**
Email : goutamchowdhury@gmail.com
Cell : 01730 453332

Received on : 15.07.2017
Accepted on : 20.07.2017

Case Report

A 35 year old Bangladeshi male hailing from Satkania, Chittagong presented with the complaints of gait instability and swellings behind both ankle joints for eight years. The swellings were painless and progressive. He had a history of bilateral cataract surgery ten months earlier. His IQ level was normal. On clinical examination, there were fusiform swellings of bilateral Tendoachilles. The swellings were firm and non-tender (Left 6×2cm, right 7.5×3 cm). On neurological examination, he had bilateral pseudophakia and both plantar responses were extensor. Romberg test could not be elicited due to contracture and spastic paraparesis. All other clinical examination revealed normal findings.

His fasting lipid profile, serum TSH, RBS, renal and liver function tests, CBC with ESR were normal. ECG, 2D Echocardiography and nerve conduction studies yielded normal findings. EEG could not be done. The serum cholestanol level was increased 7.57 mg/dl (Normal value 0.02 to 0.12 mg/dl). The blood and urinary levels of bile acid alcohols could not be measured due to unavailability of the test.

The Magnetic Resonance Imaging (MRI) was performed on a 1.5 Tesla MR scanner (Avanto, Siemens, Germany). Sequences utilised for multiplanner brain imaging were Spin-echo T1-Weighted (TR = 500ms & TE = 9.4ms) Fast Spin-echo T2-Weighted (TR = 4000ms & TE = 106ms) Fluid attenuated inversion recovery with fat saturation (TR = 9000ms, TE= 106ms & TI = 2500ms) Gradient echo (TR = 800ms, TE = 26ms) and diffusion-weighted image (TR = 3500ms & TE 102ms). Noncontrast magnetic resonance imaging of the brain demonstrated symmetrical hyperintense lesions on T2-weighted images in cerebellar dentate nuclei, that show hypo

signal intensity on Fluid-Attenuated Inversion Recovery (FLAIR) and T1-wighted images (Fig 1). Presence of confluent T2 hyper signal intensity in bilateral cerebellar white matter surrounding the dentate nuclei (Fig 2). An abnormally increased T2 & FLAIR signal was also present in the substantia nigra, cerebral peduncles, and globus pallidus with involvement of the adjacent posterior limb of the internal capsules (Fig 3). There was atrophy of the cerebellum with dilatation of the fourth ventricle (Fig 4).

For MRI of ankle swellings T1-W (TR = 600ms, TE = 14ms) T2-W (TR = 4200ms, TE = 93ms) PD (TR = 2490ms, TE = 30ms) and TRIM (TR = 3100ms, TE = 70ms, TI = 150ms) sequences were taken and show fusiform shaped thickening of the Tendoachilis having almost iso signal intensity to tendon on all sequences (Fig 5).

Brain Computed Tomography (CT) scan was done on 128 slice multidetecter scanner (Somatom AS, Siemens, Germany) and reflects the MRI findings. No calcification.

Excisional biopsies were performed for both the ankle swellings which revealed foam cells along with inflammatory cells. Giant cells surrounding the spindle-shaped cholesterol clefts were also evident on biopsy.

There was a history of childhood seizures, psychosis, visual difficulties and mental retardation in patient's younger brother who was also evaluated clinically.

Based on these clinical, biochemical, radiological and histopathological findings, the diagnosis of CTX was made. The patient was prescribed replacement therapy with CDCA 250mg 8 hourly 3 times daily and Ursodeoxycholic acid 300 mg 8 hourly 3 times daily.

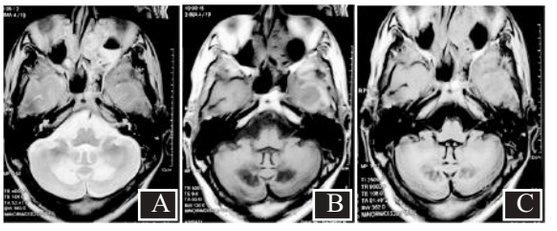

Fig 1 : Brain MRI axial sections showing symmetrical lesions in cerebellar dentate nuclei, hyperintense on T2-WI (A), hypointense on T1-WI (B) & FLAIR (C)

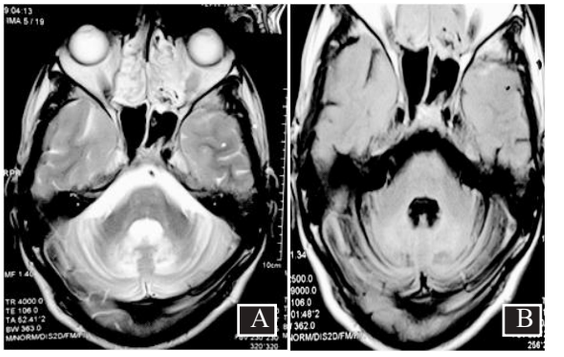

Fig 2 : MRI axial images show hypersignal intensity in bilateral cerebellar white matter. (A = T2-WI & B = FLAIR)

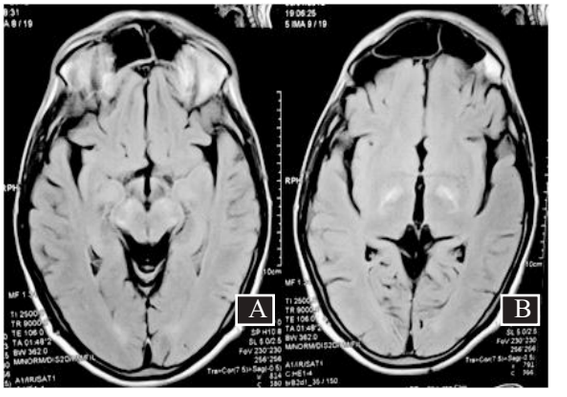

Fig 3 : Abnormal signal intensity on axial FLAIR images in bilateral substantia nigra, cerebral peduncles (A) and globi pallidi (B, arrow)

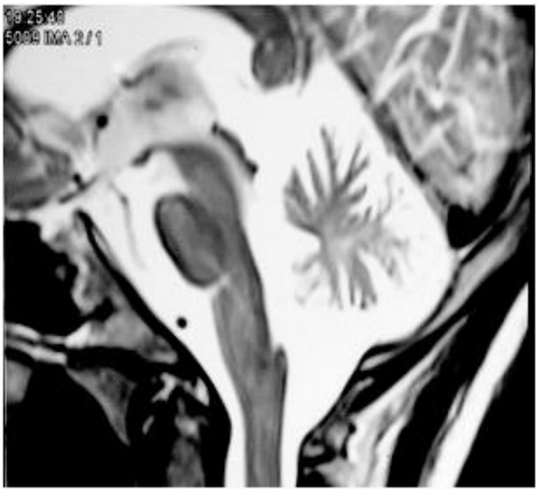

Fig 4 : MRI T2-W sagittal section showing cerebellar atrophy and fourth ventricular dilatation

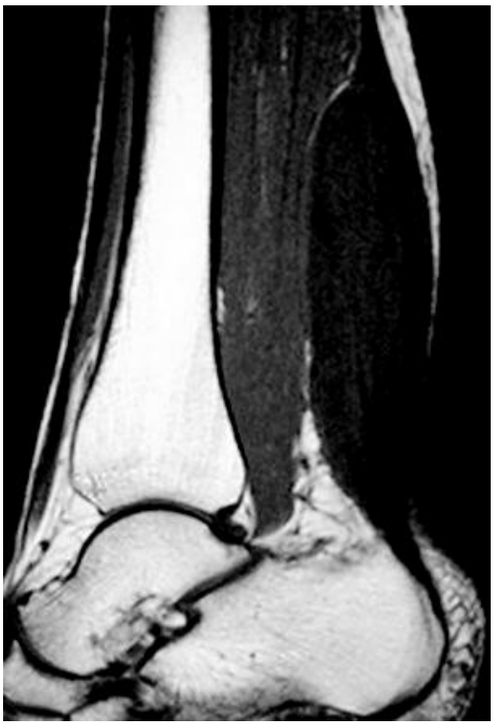

Fig 5 : Ankle MRI sagittal section T1-W image demonstrating Xanthoma of Achilles tendon

Discussion

CTX is also known as van Bogaert-Scherer-Epstein Disease which was first described in 1937 by van Bogaert[7]. So far more than 300 cases have been reported worldwide with approximately 50 mutations[4]. CTX is exceptionally rare in South Asian population with an incidence of 1:36,072 to 1:468,624[2]. The mean age of symptomatic onset for the disease is 19 years[5]. CYP27A1 gene mutation causes absent sterol 27-hydroxylase enzyme activity resulting in the ultimate deficiency of CDCA[8]. Because of the feedback inhibition loss of rate-limiting enzyme cholesterol 7-hydroxylase of bile synthesis, there is the production of cholestanol which eventually deposits in many tissues[1-3]. CTX can present with non-neurological and subtle neurological symptoms which may delay the diagnosis[1]. There may be a history of intractable childhood diarrhoea and pulmonary insufficiency alongside other classical symptoms. Significant family history may also be present[2].

Laboratory findings are also crucial for CTX diagnosis. There will be increased serum cholestanol, increased lathosterol but normal serum cholesterol. Blood and urinary bile acid alcohols may be high with low serum CDCA and 27-hydroxycholesterol[6]. MRI or CT scan can provide vital clues to the diagnosis of CTX. MRI may show focal or diffuse white matter abnormalities along with cerebral and cerebellar atrophy[1,3,10]. Tendon xanthomas are seen in MRI, CT, ultrasonogram and plain radiographs as soft tissue swelling.

Two important differential diagnoses for CTX are Sitosterolemia and Familial Hypercholesterolemia. High plasma and tissue cholestanol concentration compared to normal plasma cholesterol and low CDCA can differentiate CTX from these differentials[9]. The diagnosis of CTX may also be confused with Marinesco–Sjögren Syndrome if there are no tendinous xanthomas[10].

Replacement therapy, surgery and other symptomatic cures constellate the treatment modalities for this disease[2-5]. Replacement therapy can be given with CDCA, Ursodeoxycholic acid, Taurocholic acid and Cholic acid where CDCA is the drug of choice. This treatment can prevent or even reverse neurological complications to some extent. Sometimes for enhancing the effect of replacement therapy, HMG-CoA synthase inhibitors are also considered[1].

The patient described in this case study had all the classical features of CTX. The laboratory and histopathological findings also correlated with those of our patient's. Patient's brother was diagnosed later with the same disease. The patient was followed up at regular intervals which showed gradual improvement of the physical ailments alongside decreasing cholestanol concentration after the treatment proving the effectiveness of long-term CDCA therapy. To the authors' knowledge, a minuscule number of cases have been reported in Bangladesh as we believe in most instances CTX is misdiagnosed or underreported.

Conclusion

CTX is a rare but underreported phenomenon. It is preventable if treatment is started early. Delayed diagnosis of this disease may have devastating effects on patient's life. Long-term treatment with CDCA significantly affects the neurophysiology and improves the disease outcome. In a combination of early age bilateral cataract, tendon xanthomas and spastic ataxia this diagnosis should be suspected, and adequate replacement therapy must be initiated without any delay if tests show evidence for CTX. Although the disease is rare, the presence of the classical triad of symptoms should always raise suspicion of the potential diagnosis during clinical practice so that a healthy productive living can be ensured for the patients. Genetic testing can play a pivotal role in this regard for the prevention of disease and may reduce the associated morbidity and mortality.

Consent

The described patient provided written informed consent for publication of this case report and any accompanying images.

Disclosure

All the authors declared no competing interest.

References

1. Lorbek G, Lewinska M, Rozman D. Cytochrome P450s in the synthesis of cholesterol and bile acids from mouse models to human diseases. FEBS J. 2012;279(9):1516–1533.doi: 10.1111/j.1742-4658.2011.08432.x. [PubMed] [Cross Ref].

2. Appadurai V, DeBarber A, Chiang PW, Patel SB, Steiner RD, Tyler C et al. Apparent underdiagnosis of cerebrotendinous xanthomatosis revealed by analysis of ~60,000 human exomes. Mol Genet Metab. 2015;116(4): 298–304.doi: 10.1016/j. ymgme.2015.10.010. [PMC free article] [PubMed] [Cross Ref].

3. Ragno M, Di Marzio F, Fuccio C, Pianese L, Cozzolino V, Carboni T et al. Cerebellar hypometabolism with normal structural findings in cerebrotendinous xanthomatosis. A case report. Clin Neurol Neurosurg. 2015;139:221–223.doi: 10.1016/j.clineuro.2015.10.020. [PubMed] [Cross Ref].

4. Sandeep P, Jayakrishnan C, Sadanan S, Sreekumar S, Thulasidharan NK. Cerebrotendinous xanthomatosis: A treatable neurodegenerative disease. J Assoc Physicians India. 2009;57: 716–717. [PubMed].

5. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous xanthomatosis: A comprehensive review of pathogenesis, clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2014;9(1):179. doi: 10.1186/s13023-014-0179-4. [PMC free article] [PubMed] [Cross Ref].

6. Pilo-de-la-Fuente B, Jimenez-Escrig A, Lorenzo JR, Pardo J, Arias M, Ares-Luque A et al. Cerebrotendinous xanthomatosis in Spain: Clinical, prognostic, and genetic survey. Eur J Neurol. 2011;18(10):1203–1211.doi: 10.1111/j.1468-1331.2011.03439.x. [PubMed] [Cross Ref].

7. Chalès G, Coiffier G, Guggenbuhl P. Rare thesaurismosis and xanthomatosis. Best Pract Res Clin Rheumatol. 2011;25(5):683–701. doi: 10.1016/j.berh.2011.10.016. [PubMed] [Cross Ref].

8. Mignarri A, Magni A, Del Puppo M, Gallus GN, Björkhem I, Federico A et al. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2015;8:1–9.

9. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annu Rev Biochem. 2003;72(1):137–74.doi: 10.1146/annurev.biochem.72.121801.161712. [PubMed] [Cross Ref].

10. Jha S, Khateeb M, Sonker K. Cerebrotendinous xanthomatosis, early diagnosis mandatory: Report of a case from North India. Neurol Asia. 2008;13:125–128.