CASE REPORT

Cerebrotendinous Xanthomatosis Without Skin Changes: Diagnostic Delay and Confirmation by Genetic Analysis

SHILPA D KULKARNI, MEENAL GARG AND RAFAT SAYED
From Department of Pediatric Neurosciences, Bai Jerbai Wadia Hospital for Children, Mumbai, India.

Correspondence to: Dr Shilpa Kulkarni, EEG room, 2nd floor, Department of Pediatric Neurosciences, Bai Jerbai Wadia Hospital for Children, Parel, Mumbai 400 012, Maharashtra, India.
skulkarni.shilpa@gmail.com
Received: December 30, 2015;
Initial review: March 07, 2016;
Accepted: May 19, 2016.

Background: Cerebrotendinous xanthomatosis is an inherited lipid storage disease manifesting with infantile onset diarrhea, cataracts, xanthomas and adult-onset neurological dysfunction with cerebellar signs and neuropathy. **Case:** 10-year-old boy presented with progressive ataxia, neuropathy and cataracts. Over 6 years, he developed dementia, kyphoscoliosis with worsening ataxia, and neuropathy. **Outcome:** Sterol analysis and *CYP27A1* sequencing confirmed the diagnosis.**Message**: The condition should be considered in childhood onset cerebellar ataxia with cataracts, even in the absence of skin signs.

Keywords: *Childhood-onset ataxia; Lipid metabolism, Neuropathy*.

Cerebrotendinous xanthomatosis (CTX; OMIM#213700) is a lipid storage disease characterized by infantile-onset diarrhea, childhood-onset cataract, tendon xanthomas and adult-onset progressive neurologic dysfunction [1]. It is an autosomal recessive disorder caused by mutations in the *CYP27A1* gene located on chromosome 2q33, leading to reduced production of chenodeoxycholicacid (CDCA) and increase in cholestanol levels [2,3]. We describe a child who presented with early onset neurological symptoms without xanthomas.

CASE REPORT

A 10-year-old boy presented with progressive gait imbalance. He was the third child born of a third-degree consanguineous marriage and had two normal elder siblings. There was no family history of neurological disease. He had an uneventful birth. Mother gave history of diarrhea in the first month of life which settled after oral medication. Developmental milestones were delayed in all four domains. He had poor scholastic performance with writing difficulties. He also had a refractive error since 6 years of age and wore spectacles. There was no history of seizures. He had progressive difficulty in climbing stairs and gait imbalance since 8 years of age. He had recently started having falls while walking. On examination, he was able to understand and follow simple instructions. His height was 120 cm (less than 3rd percentile) and head circumference was 51 cm (between 10th and 25th percentile). There were no skin lesions. He was noted to have bilateral developmental cataracts. Speech was slurred but understandable, and cranial nerve examination was normal. There was high stepping gait and bilateral pes cavus. Deep tendon reflexes were depressed, power was 4/5 in proximal muscles and 3/5 in distal muscles. Cerebellar signs were predominant including ataxia, dysmetria, intention tremors and dysdiadokinesia. Romberg's sign was positive.

Patient was first investigated to rule out treatable causes of chronic progressive ataxia (Vitamin E levels, peripheral smear, fasting lipid profile, lactate levels, etc). Lipid profile was normal with cholesterol of 170 mg/dl (normal levels-122-228 mg/dL). Differential diagnoses of cataracts with progressive ataxia were considered at this point, including Friedreich ataxia, Marinesco-Sjogren syndrome, CTX and Congenital Cataracts with Facial Dysmorphism and Neuropathy. Echocardiogram was normal. Magnetic Resonance Imaging (MRI) of the brain showed bilateral parieto-occipital white matter abnormalities with dentate nucleus hyperintensities (***Fig.*1**). Nerve conduction studies suggested symmetrical sensorimotor demyelinating polyneuropathy. He was treated symptomatically without any benefit. Sequencing of *FXN* gene for Friedreich ataxia did not reveal any pathogenic variation. Further biochemical and genetic testing could not be carried out owing to financial constraints.

The patient was followed up for six years. Ataxia and slurring of speech slowly worsened. Cataracts were operated. He developed dementia and dropped out of school. There was appearance of kyphoscoliosis along with

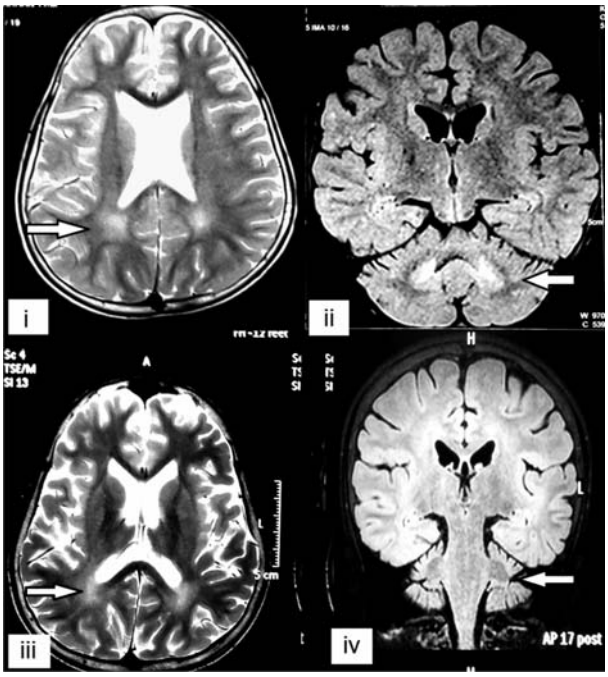

FIG. 1 *(i). T2-weighted axial section of MRI brain showing parieto-occipital white matter hyperintense signal. (ii). Fluid attenuated inversion recovery (FLAIR) coronal section showing dentate nucleus involvement and cerebellar atrophy. (iii). T2-weighted axial section of MRI brain done 4 years later showing increase in parieto-occipital white matter hyperintense signal and cortical atrophy (iv). FLAIR coronal section showing increase in dentate nucleus involvement and cerebellar atrophy.*

distal wasting, increasing pes cavus and new onset dystonia. *X*-rays did not show any significant abnormality except spinal deformity. Dual energy *X*-ray absorptiometry scan showed a Z score of -4.0 (lower than normal). Pulmonary function tests were normal. MRI of the brain repeated after four years showed worsening of the changes in dentate nucleus and white matter with cerebellar atrophy (***Fig.* 1**). Sterol analysis revealed high cholestanol (69.98 umol/L, normal value: 0.04-9.31 umol/L), normal cholesterol (1,916.97 umol/L; normal value: 1050-3229 umol/L) and cholestanol:cholesterol ratio of 0.03651 (normal: ~0.0051). Sequencing of the *CYP27A1* gene was performed and showed c.525delG homozygous mutation resulting in a frameshift and premature truncation of the protein. This is a previously reported mutation in a patient with CTX [4] and was confirmatory of the clinical suspicion. The parents were advised genetic testing but were unwilling in view of financial concerns. Genetic testing for siblings has been advised.

DISCUSSION

Patients with CTX lack the mitochondrial enzyme sterol 27-hydroxylase leading to reduced levels of CDCA and up regulation of the enzyme precursors of bile acid formation pathway and cholestanol. Neurological involvement is seen in adolescents and adults in the form of cerebellar and supratentrorial symptoms, myelopathy, epilepsy, parkinsonism, psychiatric manifestations and peripheral neuropathy. Cardiopulmonary disease and osteoporosis are other features [6].

Our patient presented with early onset ataxia, cataracts and neuropathy. Treatable causes such as abetalipoproteinemia, vitamin B_{12} and vitamin E deficiencies were ruled out. Friedreich ataxia was considered as it is one of the most common causes of recessively inherited ataxia and has myriad presentations. Marinesco-Sjogren syndrome can also present with early onset cataracts, cerebellar signs, cerebellar atrophy and psychomotor retardation, but patients have early onset myopathy. Congenital contract with facial dysmophism and neuropathy similarly presents with cataracts, neuropathy, late onset cerebellar signs, short stature and mild facial dysmophism; our patient did not have dysmorphic features or significant anterior chamber abnormalities.

Early onset of cerebellar signs with polyneuropathy without xanthomas has been rarely described in CTX. Due to the absence of xanthomas, there was a delay in the diagnosis. A strong possibility was reconsidered after application of clinical suspicion index [7], but could not be confirmed at the time.

CTX should be considered as a differential diagnosis of chronic progressive ataxia in pediatric age group. Cataracts and early refractory diarrhea may act as important clues. Xanthomas may develop later in the course. A multidisciplinary treatment approach and use of CDCA and statins is recommended. Genetic counseling and testing for asymptomatic members should be offered to the family.

Contributors: SDK, MG: data acquisition; SDK, MG: literature research; SDK, MG, RS: manuscript preparation; SDK, MG, RS: manuscript editing and revision. All authors have read the manuscript and approved the final version.
Funding: None; *Competing Interest*: None stated.

REFERENCES

1. Federico A, Dotti MT, Gallus GN. Cerebrotendinous Xanthomatosis. *In*: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, *et al*., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.
2. Cali JJ, Hsieh CL, Francke U, Russell DW. Mutations in the bile acid biosynthetic enzyme sterol 27-hydroxylase underlie cerebrotendinous xanthomatosis. J Biol Chem. 1991;266:7779-83.

3. Fraidakis MJ. Psychiatric manifestations in cerebrotendinous xanthomatosis. Transl Psychiatry. 2013;3:302.
4. Verrips A, Steenbergen-Spanjers GC, Luyten JA, van den Heuvel LP, Keyser A, Gabreëls FJ, *et al*. Two new mutations in the sterol 27-hydroxylase gene in two families lead to cerebrotendinous xanthomatosis. Hum Genet. 1996;98:735-7.
5. 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;18:1203-11.
6. 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;9:179.
7. Mignarri A, Gallus GN, Dotti MT, Federico A. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. J Inherit Metab Dis. 2014;37:421-9.