Cerebrotendinous Xanthomatosis: A Rare Etiology of the "Hot-Cross Bun" Sign

Divya Rani, Deepshikha Singla, Divyani Garg[1]

Department of Neurology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, [1]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Clinical Information

A 26-year-old female presented with chronic diarrhea with onset at the age of 3 years. At 22 years, she was operated for bilateral cataracts. Subsequently, she complained of insidious, progressive gait ataxia from the age of 24 years, accompanied by cognitive impairment. There was no significant family history. On examination, she had bilateral pseudophakia. Tendon xanthomas were observed over bilateral Achilles tendon. She had distal lower limb wasting with pes cavus [Figure 1a and 1b]. Higher mental function assessment showed impairment of complex attention, calculation, semantic, and recent memory. She had brisk deep tendon reflexes with absent ankle jerks. Cerebellar signs were prominent, including titubation, impaired finger–nose–finger and heel–knee–shin test, dysdiadochokinesia, intention tremor, and gait ataxia.

Evaluation showed normal hemogram, renal, hepatic, thyroid function, and serum vitamin E and B_{12} levels. Nerve conduction study showed sensorimotor demyelination with secondary axonal changes. Bone mineral density scan showed osteoporosis. Magnetic resonance imaging (MRI) of the brain showed striking T2 hyperintensity and blooming of the dentate nuclei with a pontine hot-cross bun and enlarged Virchow–Robin spaces [Figure 2a-c]. Sanger sequencing of *CYP27A1* gene showed a pathogenic homozygous c.1421G>A (p. Arg474Gln) variant in exon 8, confirming the diagnosis of cerebrotendinous xanthomatosis (CTX). The patient was initiated on ursodeoxycholic acid (due to unavailability of chenodeoxycholic acid), alendronate, calcium, cholecalciferol supplements, and physiotherapy.

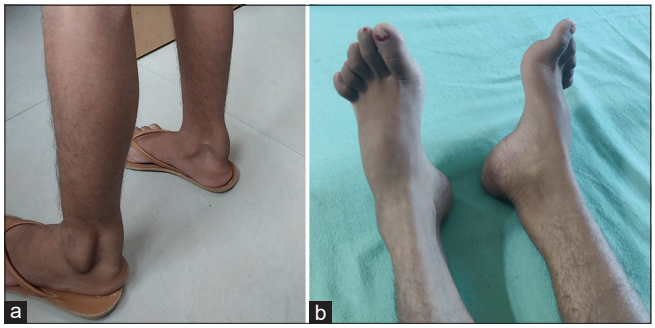

Figure 1: (a) Tendon xanthomas seen overlying bilateral Achilles tendon and (b) thinning of the distal lower extremity with pes cavus

Discussion

CTX (#OMIM 213700) is a rare lipid storage disorder.[1] Although an autosomal recessive condition due to *CYP27A1* mutations, it is treatable. *CYP27A1* encodes the mitochondrial enzyme sterol 27-hydroxylase, which enables bile acid synthesis. A deficiency/absence of sterol 27-hydroxylase reduces cholic and chenodeoxycholic acid levels. Consequently, cholesterol is not converted to bile acid, but to cholestanol and bile alcohol.[2]

Radiological features in CTX are characteristic and include symmetric T2-weighted dentate nucleus hyperintensities, white matter involvement, and cerebellar and cerebral atrophy, seen in up to 84% of patients.[3] Periventricular white matter, posterior limbs of internal capsule, cerebral peduncles, anterior pons, inferior olive, and the cerebellar white matter may also be involved.[4] Over time, FLAIR hypointensities on T2/FLAIR and SWI in dentate nuclei may develop due to hemosiderin deposition, microcalcification, or cystic necrosis. A spinal form of CTX, involving the central and posterior cord, has also been reported. The radiological differentials of CTX include Marinesco–Sjogren syndrome; however, tendon xanthomas are not seen. The other differential is myotonic dystrophy type 1, in which muscle weakness is prominent.

The presence of the "hot-cross bun" sign, as seen in this patient, has been extremely rarely reported in association with CTX. Previously, it was reported in a patient, a 25-year-old male with clinical and radiological features similar to our patient.[5] The "hot-cross bun" sign is named after a spiced fruity bun eaten on Good Friday, which is baked with a cross-marked at the top. It has been considered synonymous with multiple

Address for correspondence: Dr. Divyani Garg, Assistant Professor, Department of Neurology, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: divyanig@gmail.com

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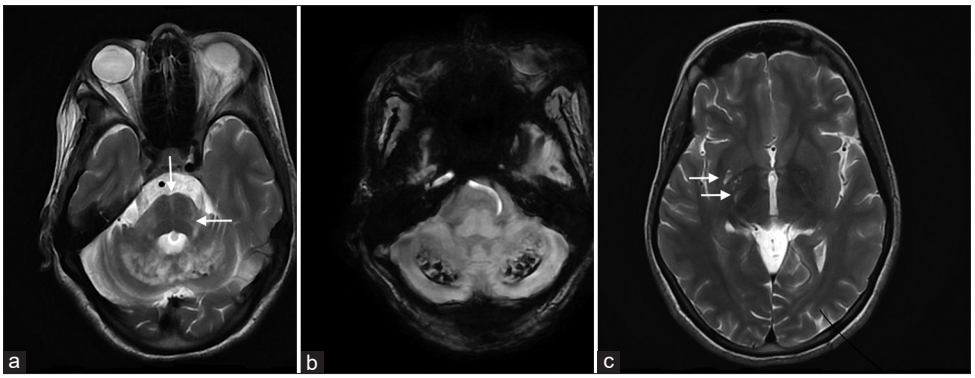

Figure 2: (a) T2-weighted axial MRI showing hyperintensities admixed with hypointensities in the dentate nuclei, along with the pontine "hot-cross" bun sign (arrows marking the degeneration of the transverse pontine and median raphe fibers) and bilateral middle cerebellar peduncle hyperintensities. (b) SWI axial imaging showing blooming in the dentate nuclei. (c) Enlarged Virchow–Robin spaces in the lower right basal ganglia (arrow)

system atrophy (MSA), although case reports have emerged in association with several other diseases, including spinocerebellar ataxias, fragile-X tremor–ataxia syndrome, HIV-related progressive multifocal leukoencephalopathy, neurosarcoidosis, pontine infarction, and variant Creutzfeldt–Jakob disease.[6] The cross-like appearance is believed to be due to loss or degeneration of two fiber groups: the transverse portion of the cross is due to degeneration of the transverse pontocerebellar fibers, and the vertical portion is due to degeneration of the median pontine raphe fibers. Characteristically, the pontine tegmentum and corticospinal tracts remain preserved, giving rise to this "crossed" appearance. Middle cerebellar peduncle hyperintensities on T2/FLAIR may be seen in several disorders, namely, MSA, fragile X-tremor–ataxia syndrome, multiple sclerosis, ischemia, and spinocerebellar ataxias.

Our case highlights a rare radiological feature of CTX and expands the spectrum of disorders associated with the "hot-cross bun" sign.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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