Cerebrotendinous xanthomatosis

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Introduction

Cerebrotendinous xanthomatosis is a rare genetic metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurologic abnormalities. Typically, the disease begins in infancy with chronic diarrhoea. Cataracts become evident in childhood or adolescence, and xanthomata develop in the second and third decades of life. Significant neurologic impairment also occurs; this often includes seizures, dementia, and extrapyramidal dysfunction and typically begins in the third decade of life and progresses until death, often in the sixth decade of life if the condition goes untreated. The disease was first described in 1937 by Van Bogaert and colleagues[1] and since then only a handful of cases have been published in literature.Here we report a 15 year old male child presenting with typical features of cerebrotendinous xanthomatosis.

Case report

A 15 year old boy was referred for evaluation of progressive dementia and abnormal gait. His birth and development were normal, except that he had intractable diarrhoea during childhood. He attended school education only up to third class of primary school and left the school because of learning problems. His parents recognized that he had mental insuffiency, poor attention and concentration with impaired memory and with the passage of time these findings became more evident. Further, nodular thicknesses on his Achilles tendons were recognized by his family when he was 7 years old, and they became larger within years. Their colour was grayish yellow and they were painless. Cataracts were found at age 10 and his walking became unsteady at age 12. There was no family history of neurological or systemic illness. Xanthomas on the Achilles tendons and high arched feet were detected on physical examination (Figure 1).

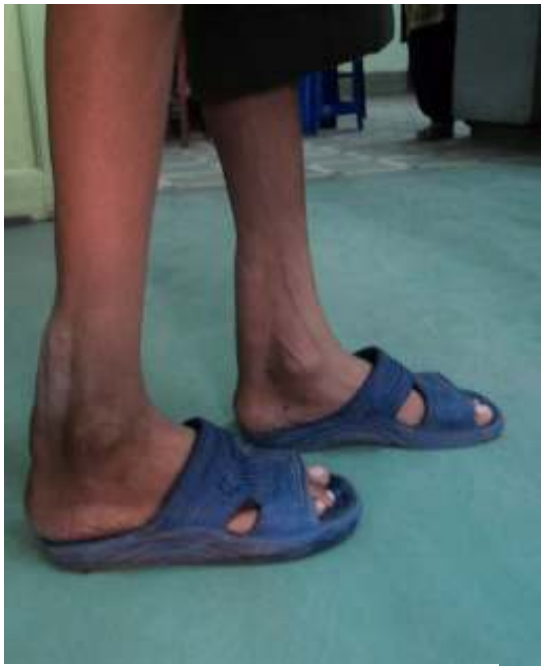

Figure 1: ***Xanthomas on the Achilles tendons***

His neurological examination showed mental insufficiency with subnormal Mini-Mental Status Score (22/30), mild spasticity in the lower extremities, normal power, diffuse hyperreflexia, moderate truncal ataxia, stocking distribution sensory loss to light touch and loss of proprioception in the legs. Laboratory tests revealed normal total plasma cholesterol, LDL cholesterol and triglycerides but plasma cholestanol level could not be done. Electrocardiography, echocardiography, abdominal ultrasonography (USG) and thorax computer tomography (CT) were normal. Electromyography (EMG) and nerve conduction velocity (NCV) revealed sensorimotor neuropathy. Magnetic resonance imaging (MRI) study of Achilles tendons showed a diffuse enlargement of the tendon from musculotendinous junction to calcaneal insertion, and also showed heterogenous hypointensity signal on T1 and T2 images (Figure 2).

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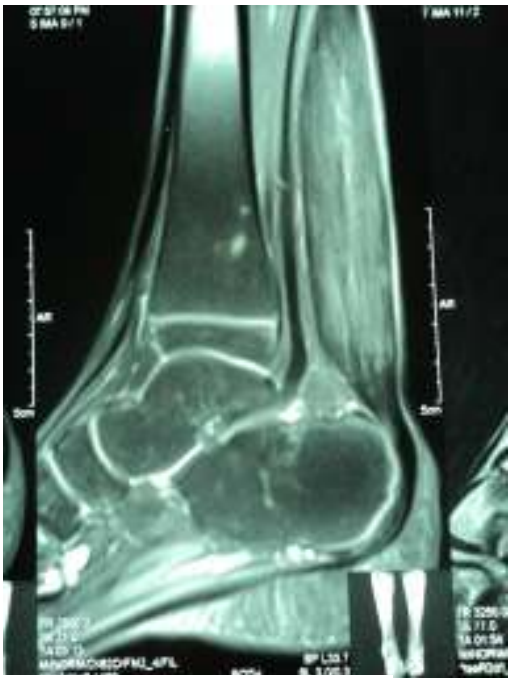

Figure 2: ***MRI of Achilles tendon***

A biopsy of the ankle lesions revealed multiple foam cells with eccentric nuclei admixed with fibrotic areas suggestive of xanthomas (Figure 3).

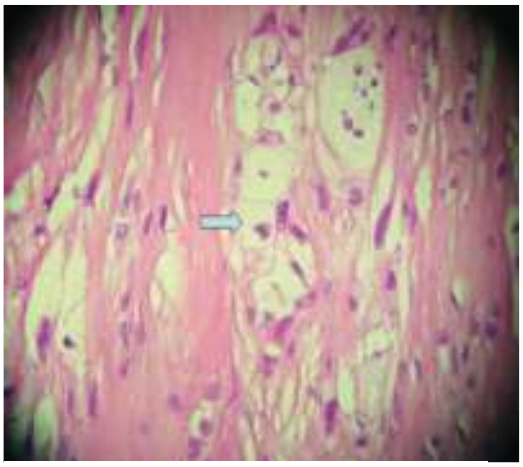

Figure 3: ***Biopsy of muscle showing foam cells***

With these physical, radiological and biochemical findings the patient was diagnosed as cerebrotendinous xanthomatosis (CTX). He was treated with chenodeoxycholic acid. His gait improved with the treatment but there was no improvement of intellectual function.

Discussion

Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid storage disease with prominent neurological features. The disease was first described by Van Bogaert at el. in 1937[1]. The disease is associated with accumulation of cholestanol in many tissues due to loss of mitochondrial sterol 27-hydroxylase enzyme function. This leads to formation of multiple xanthomas of tendons and other tissues, dementia, premature cataracts, progressive cerebellar ataxia, spinal cord paresis, peripheral neuropathy and chronic diarrhoea[2]. Achilles tendon is the most common site of tendon xanthomas, but quadriceps, triceps and finger extensor tendons can also be involved.

Our patient presented with almost all the symptoms of the disease. He had intractable diarrhoea during childhood. Cataracts were found at age 10. Xanthomas were recognised when he was 7 years old. He had learning problems and was unsuccessful at school. The clinical pattern was characterized by progressive dementia and abnormal gait. Onset of the disease usually occurs toward the end of the first decade of life, and most individuals live beyond middle age[2]. Early onset cataracts are characteristic of cerebrotendinous xanthomatosis. Besides cataracts, the second most frequent ocular abnormality is pallor of the optic disc[3]. Cataracts were found in our patient at age of 10; no other abnormality was observed in her ophthalmological examination. Peripheral neuropathy is a prominent feature of cerebrotendinous xanthomatosis as evidenced by pes cavus deformities, loss of deep tendon reflexes and loss of vibration perception[4]. Stocking distribution sensory loss to light touch and loss of proprioception in the legs were detected on our patient's neurological examination and his EMG NCV was compatible with sensorimotor neuropathy. Seizures are encountered in 40-50% and can be presenting symptom[2]. As seen in our patient during childhood period intractable diarrhoea can be a nearly major manifestation[5,6]. He did not have any epileptic seizure.

Biochemical changes are very important for the diagnosis of CTX. The cholesterol and triglyceride concentrations in serum are normal but cholestanol levels in serum and erythrocytes are elevated. Levels of cholestanol are particularly high in bile, xanthomas and brain[7,8]. Also neuroradiological studies can be used for the diagnosis of CTX. Magnetic resonance imaging findings typically include bilateral and almost symmetrical increase of the signal intensity on the T2-weighted images in the cerebellar and periventricular cerebral white matter, the basal ganglia, the dentate nuclei and the brainstem as well as cerebellar and cerebral atrophy[9]. MR study of Achilles tendon shows a diffuse enlargement of the tendon with multiple areas of signal changes on T1 and T2 demonstrative of the lipid deposits, interposed between the isosignal zones, they may correspond

to the inflammatory reaction secondary to the accumulation of cholesterol and cholestanol[10]. Our patient's Achilles tendon MR study showed heterogenic hypointensity signal on T1 and T2 images and cystic degeneration compatible with CTX. Early diagnosis is imperative in CTX, as the pharmalogical treatment with chenodeoxycholic acid (or with a combination of chenodeoxycholic acid and HMG-CoA reductase inhibitors) has been shown to slow or even reverse the progression of the disease. Treatment with chenodeoxycholic acid has been reported to be beneficial in some patients who showed a correction of biochemical abnormalities, a reversal of neurological symptoms, and an improvement in somatosensory evoked potentials and in the MRI scan[11]. We used chenodeoxycholic acid for treatment and minimal improvement of gait pattern was observed but no improvement was found in his intellectual functions.

CTX is a rare progressive lipid storage disease with prominent neurological features. Physicians should be aware of possible clinical, physical manifestations and neurological findings; because early diagnosis and treatment may reduce the risk of long term neurologic sequelae.

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