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Cerebrotendinous xanthomatosis, early diagnosis mandatory: Report of a case from North India

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Abstract

A 30 year old male presented with insidious onset of painless swellings in tendons over 20 years, with learning difficulty, tremors, progressive instability of gait and frequent falls. There was no similar illness in family. On examination, there was firm, non tender, nodular swelling Achilles, patellar and tricep tendon, clubbing of fingers. The Mini Mental Status Examination score was 16/30. Plantar response was extensor. There was cerebellar signs with nystagmus, truncal titubation, ataxic gait and intentional tremors. Cranial MRI showed bilateral hyperintensities in dentate nucleus, globus pallidus, periventricular white matter on FLAIR/T2 sequences, and diffuse cerebral and cerebellar atrophy. The patient was diagnosed as having cerebrotendinous xanthomatosis based on the clinical and radiological features. As cerebrotendinous xanthomatosis benefit from therapy and progress of the disease is preventable, the case illustrates the need for early diagnosis.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare disorder with autosomal recessive inheritance, characterized by accumulation of cholestanol and cholesterol, predominantly in the brain, spinal cord, peripheral nerves, tendons, lungs, liver and kidneys. Juvenile cataract, mental retardation, cerebellar ataxia and swelling of the tendons are the most prominent features of this disease.[1,2] Early diagnosis is important, as patients benefit from therapy and the progress of the disease can be prevented.[3] We present clinical and radiological features of a 30 year old male with CTX, which is rare in the Indian population.[4,5]

CASE REPORT

A 30 year old male reported in the neurology out patient station with complaints of insidious onset of painless, gradually increasing swellings along the course of both achilles and patellar tendons over last 20 years. Similar swelling was noted for last 10 -11 years over left elbow region. The patient had history of irritable behavior and poor scholastic performance with learning difficulty. He dropped out from school after seventh standard. There was history of tremors along with progressive instability of gait, so that he was unable to walk on uneven surface for last 8-10 years. This difficulty in walking increased markedly for last 2 years, resulting in frequent falls. He also had progressive diminution of vision in both eyes due to cataract, for which he was operated in right eye, about a year back. There was history of frequent attacks of diarrhea (3-4 times a month) during childhood. He was youngest of four siblings. There was no history of consanguinity or similar illness in family.

On examination, firm, non tender, nodular swelling, ranging from 5-8 cm in diameter were present on achilles and patellar tendon bilaterally, and tricep tendon on the left side (Figure 1, 2). Clubbing of fingers was present bilaterally.

The cardio-thoracic and abdominal examination was clinically normal. Patient was fully conscious, alert, cooperative but mentally retarded (IQ = 64). He had a Mini Mental Status Examination score of 16/30. Right eye was aphakic with normal fundus. Media of left eye was hazy due to cataract. Motor examination revealed normal motor power with brisk tendon jerks. Plantar response was extensor. Bilateral cerebellar signs including gaze evoked nystagmus, truncal titubation, ataxic gait and intentional tremors were present.

The hematological and biochemical profile including hepatorenal, pancreatic and lipid profile was normal. The ECG tracing showed T wave inversion in lead III and aVF with features suggestive of right ventricular hypertrophy (tall R wave in V1). The nerve conduction studies and electromyography was normal. Cranial MRI was done on Sigma 1.5 T Gemson system where

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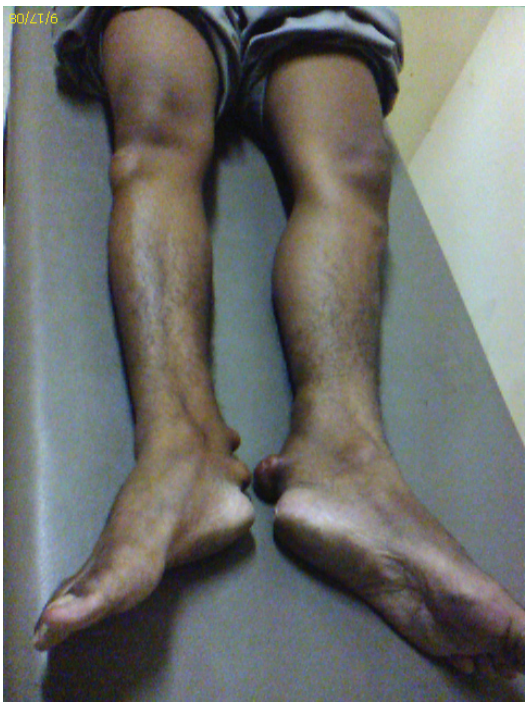

Figure 1. Xanthomas in the patellar and Achilles tendons.

Figure 2. Xanthoma in left triceps tendon.

T_1 weighted images showed hypointensities in cerebellar white matter and outgoing tract of dentate nuclei. The T_2 weighted images showed bilateral hyperintensities in dentate nucleus, (Figure 3) and globus pallidus, with periventricular white matter hyperintensities on FLAIR sequences (Figure 4). Diffuse cerebral and cerebellar atrophy was present.

DISCUSSION

We made the diagnosis of CTX based on clinical and radiological features. Approximately 300 cases of CTX have been reported worldwide, but probably the incidence is underestimated.[6] The disease is attributed to approximately 50 mutations in the *CYP27A1* gene coding for the hepatic oxidation of the side chain of the cholesterol molecule in bile acid biosynthesis. Its deficiency decreases bile acid synthesis. This reduces feedback inhibition on cholesterol 7-alpha hydroxylase, resulting in synthesis and accumulation of more cholestanol.[7,8]

Clinical presentations may vary considerably in CTX, but no genotype–phenotype relationship has been documented. Patients usually present in childhood or early adult life. Tendon xanthomas, especially over the achilles tendon are characteristic of the disorder and clinically resemble those seen in familial hypercholesterolemia or hyperlipoproteinemia but biochemical analysis reveal that they contain high amounts of cholestanol and little cholesterol.[2,9] Other reported manifestations include mental retardation, juvenile cataract[2,8,10], abnormal behavior[9], and premature arteriovascular disease.[11] Association of bilateral juvenile cataracts with chronic diarrhea may represent the earliest clinical manifestation of CTX, as evident in our case. In absence of tendon xanthomas, CTX may be confused with Marinesco –Sjoegrenn syndrome.[12] Our patient had tendon xanthomas, juvenile cataract, behavior abnormalities and progressive neurological symptoms mainly of cerebellar origin, features suggestive of CTX. He also had irritability, depressed mood, insomnia, and fatigability as the psychiatric manifestations, which may occur in patients with CTX.[9]

Several patients with CTX develop premature atherosclerosis and consequent cardiac events including myocardial infarction, which is a serious concern. Atherosclerotic aneurysms in coronary arteries of patients with CTX have been described. Whether aneurysmal rather than obstructive coronary artery disease is more characteristic

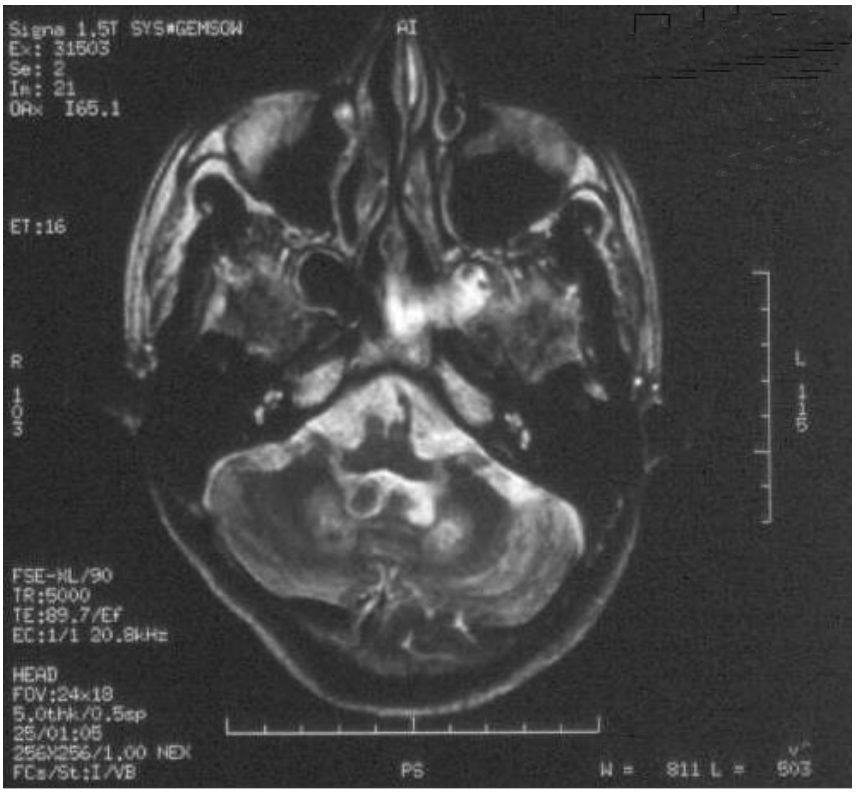

Figure 3. The T_2 weighted cranial MRI revealing bilateral hyperintensities in dentate nucleus.

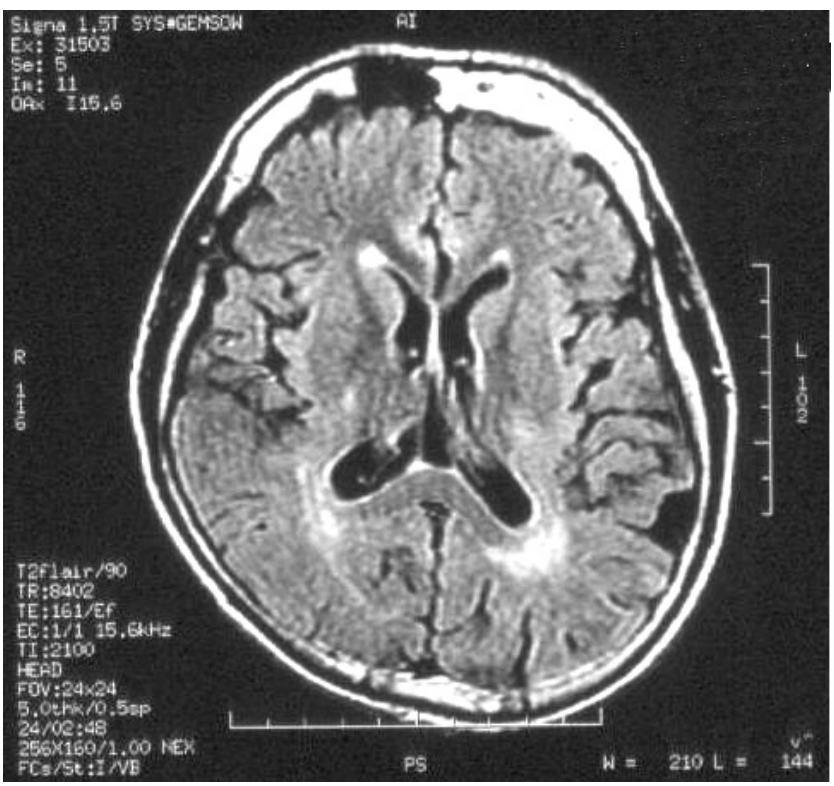

Figure 4. The MR images revealing periventricular white matter hyperintensities on FLAIR sequences.

of CTX, is unknown. Fortunately in our patient the ECG revealed no frank evidence of ischemia except for features of right ventricular hypertrophy. Therefore, it is strongly recommended that in CTX the presence of cardiovascular disease should be investigated even in asymptomatic patients.[11,13]

Conventional MRI studies are sensitive for diagnosis and have shown focal/ diffuse white matter abnormalities and different degrees of cerebral and cerebellar atrophy in patients with CTX. The bilateral nonhomogenous, hyperintense magnetic resonance signal in dentate nuclei and surrounding cerebellar white matter, can be considered as a neuroradiological feature suggestive of CTX and could become an important diagnostic marker.[4,14,15] These characteristic changes were present in our case.

Several modes of treatment have been forwarded for CTX. Since 1975, chenodeoxy cholic acid (750 mg daily) has been commonly used as the standard therapy, which influences the negative feedback of cholesterol and bile acid synthesis. There is a considerable decrease in the serum cholestanol and a sharp decline in the excretion of urine bile alcohols which is associated with improvement in the clinical symptoms. [16,17,18] Removal of the achilles tendon xanthomas may be considered for cosmetic reasons, but it may worsen the gait. Long-term treatment may arrest or even reverse the progression of the disease, which may coincide with the normalization of plasma and cerebrospinal fluid cholestanol levels.[18]

The need for early diagnosis is well documented in the literature, as it prevents significant morbidity and mortality associated with this disease.[3,4,17] Unfortunately, as in our case, the disease is not usually diagnosed before the second or third decade of life and at this stage cholestanol has already been extensively deposited in many tissues. Therefore, early diagnosis of this rare metabolic disease is mandatory and CTX should be considered in every patient with intellectual impairment, spastic - ataxic signs, juvenile cataract and tendon xanthomas and MR imaging should be done as soon as possible.

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