

## Difficulties in Diagnosis and Treatment of a Case of Cerebrotendinous Xanthomatosis (CBX)

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### Abstract

The tendon pathology is very complex including traumatic, inflammatory and storage disorders. Cerebrotendinous Xanthomatosis (CBX) is a rare lipid storage disorder, characterized by the accumulation of fats in various areas of the body (mainly central nervous system and tendons). A mutation in the CYP27A1 gene leads to a deficient break down of cholesterol, who is responsible to the formation of a molecule called cholestanol which accumulates in different tissues. We present the case of a young woman presenting with bilateral Achilles tendon painful swelling and mild mental retardation.

### Key words:

Cerebrotendinous xanthomatosis; Tendon swelling; Mental retardation

### Background

Cerebrotendinous xanthomatosis (CTX) is a rare lipid storage disorder, characterized by the accumulation of fats in various areas of the body. The first description of the disease was in 1937 by Van Bogaert [1]. This condition has autosomal-recessive transmission and is due to a mutation in the CYP27A1 gene located on chromosome 2q [2]. The CYP27A1 encodes an enzyme – sterol 27-hydroxylase - which breaks down cholesterol to a specific bile acid called chenodeoxycholic acid. A mutation in the CYP27A1 gene leads to a deficient break down of certain lipids, mainly different forms of cholesterol. This leads to the formation of a molecule called cholestanol which accumulates in different areas of the organism. Serum levels of cholesterol are normal, but an increased deposition of cholesterol in various tissues is also found in CTX [2-5]. The incidence of CTX is estimated to be 3 to 5 per 100000 people worldwide [2]. The main clinical manifestations appears in the childhood. Cataract with childhood onset is one the earliest and specific manifestation of CTX. Neurological manifestations as epilepsy and Parkinsonism are also early symptoms of the disease, and some other neurological manifestations as intellectual disability, depression, ataxia could develop later. Prolonged neonatal jaundice, chronic, intractable diarrhea, starting from childhood, and also premature atherosclerosis are very frequent. Osteoporosis and tendinous xanthoma are the most frequent musculoskeletal manifestations but not all the patients will develop clinically manifest xanthoma and it is important to remember that tendinous xanthoma it is not usually an early manifestation of CTX [2-5].

The criteria used for diagnosis include intractable diarrhea, presenile cataracts, tendinous xanthomas, and neurological abnormalities [2-5].

The treatment of choice is chenodeoxycholic acid because it is reducing effectively the seric levels of cholestanol and the neurological and non-neurological manifestations of the disease [2-5]. Some other bile acids as ursodeoxycholic acid or cholic acid have been used and cholic acid seems to be effective for non-neurological symptoms of CTX. The treatment with statins alone is controversial but the association of chenodeoxycholic acid and statins is effective and seems to add efficacy compared to chenodeoxycholic acid alone [2-5]. The treatment will slow, stop or even revers the symptoms of CTX depending of the time of diagnosis and beginning of the treatment [2].

### Case Presentation

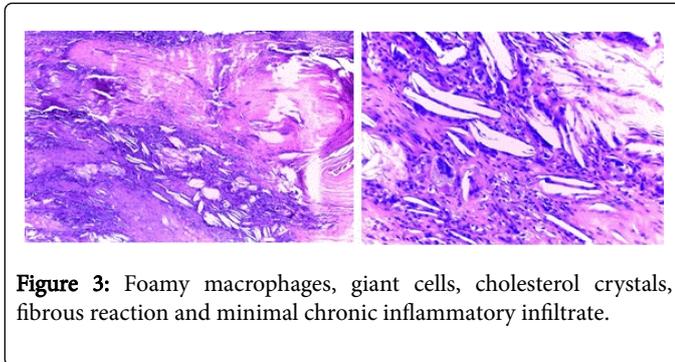
We present the case of a 29 years old female, admitted for bilateral Achilles tendon painful swelling lasting for 6 month, loss of appetite, weight loss and memory disorders. From her medical history we noticed prolonged neonatal jaundice, surgery for bilateral cataract and chronic diarrhea during infancy.



Figure 1: Bilateral swollen Achilles tendon.



**Figure 2:** Musculoskeletal imaging with markedly swollen tendon with inhomogeneous and predominantly hypoechoic appearance.



**Figure 3:** Foamy macrophages, giant cells, cholesterol crystals, fibrous reaction and minimal chronic inflammatory infiltrate.

At the physical examination she is underweight (38 Kg), with mild mental retardation, bilateral swelling of the Achilles tendon and limited dorsal flexion of the feet (Figure 1). Laboratory tests show normal serum cholesterol=138.27 mg/dl and serum cholestanol=3.6 mg/dl.

Musculoskeletal ultrasound imaging identifies diffuse tendon swelling close to the calcaneal insertion. We performed Achilles tendon biopsy and the aspect foamy macrophages, cholesterol crystals, giant cells, fibrous reaction and minimal chronic inflammatory infiltrate (Figure 2 and 3). The treatment was with chenodeoxycholic acid 750 mg QD.

## Conclusion:

Even if this patient presented symptoms since childhood, they were considered nonspecific and did not lead to the actual diagnosis of CTX at that moment. It is important to increase the awareness of the general practitioners and pediatricians about the possibility of a congenital lipoproteins metabolic disorder in the presence of the association of ocular, neurological and digestive manifestations from the early childhood.

The delay in establishing the diagnosis and initiating therapy led to irreversible mental retardation. Data suggest that even if treatment is initiated after the onset of mental deficit, the damage is irreversible [2].

The differential diagnosis is complex and is based on clinical manifestations, the determination of serum cholestanol, biopsy and genetic tests. It includes hypercholesterolemia type II, leukodystrophies, xanthomas, other bile acid synthesis and conjugation disorders [2].

For the earlier diagnosis of CTX Mignarri et al proposed a suspicion index: tendon xanthomas were regarded as very strong indicators [6], but unfortunately it is not early manifestation and in order to prevent irreversible neurological manifestations it is essential to begin early treatment with chenodeoxycholic acid [2-6].

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