

CASE REPORTS

Cerebrotendinous Xanthomatosis: Report of 4 Patients

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Abstract. Cerebrotendinous xanthomatosis (CTX) is an uncommon autosomal recessive disease caused by mutation of the *CYP27A1* gene. It is characterized by the presence of xanthomas in different tissues, principally brain and tendon, due to the accumulation of β -cholestanol. Diagnosis is confirmed by measurement of serum β -cholestanol and urinary bile alcohol levels. Therapy with chenodeoxycholic acid has been shown to be the most effective treatment and can halt progression of the disease. We present 4 patients with a history of neurological disorders since childhood and who were diagnosed with CTX after developing tendon xanthomas. Although diagnostic suspicion depends to a large extent on recognition of tendon xanthomas, these are not an early sign of the disease, which can present with neurological disorders, cataracts, and chronic diarrhea. Early diagnosis of CTX therefore rests on measurement of serum β -cholestanol levels, even in absence of tendon xanthomas.

Key words: cerebrotendinous xanthomatosis, tendon xanthoma, chenodeoxycholic acid, sterol 27-hydroxylase, cholestanol.

XANTOMATOSIS CEREBROTENDINOSA: DESCRIPCIÓN DE 4 CASOS

Resumen. La xantomatosis cerebrotendinosa (XCT) es una enfermedad hereditaria infrecuente causada por la mutación del gen *CYP27A1*. Es característica la aparición de xantomas en diferentes tejidos, principalmente en el cerebro y los tendones, secundarios al depósito de β -colestanol. El diagnóstico se confirma mediante la determinación de β -colestanol en suero, y de los alcoholes biliares en orina. El ácido quenodesoxicólico es la terapia más eficaz, pudiendo llegar a frenar la progresión de la enfermedad. Presentamos 4 pacientes con alteraciones neurológicas desde la infancia que fueron diagnosticados de XCT tras el desarrollo de xantomas tendinosos. El reconocimiento de los xantomas tendinosos es fundamental para orientar el diagnóstico de XCT, pero estos no son un signo inicial de la enfermedad, que debuta con alteraciones neurológicas, cataratas o diarrea crónica. Por lo tanto, el diagnóstico temprano de la XCT requiere la determinación del β -colestanol sérico en estos pacientes, aun en ausencia de xantomas.

Palabras clave: xantomatosis cerebrotendinosa, xantoma tendinoso, ácido quenodesoxicólico, 27-esterolhidroxilasa, colestanol.

Introduction

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder caused by sterol-27 α -hydroxylase deficiency.^{1,2} Mutations in the gene that encodes

this enzyme (*CYP27A1*) are responsible for the disease, which is characterized by the formation of xanthomas in different tissues, particularly the brain and tendons.^{3,4} Biochemical diagnosis is made when elevated levels of serum β -cholestanol and urinary bile alcohols are detected. Molecular study of the gene can identify heterozygotes and provide prenatal diagnosis.^{5,6} Early diagnosis is essential to initiate treatment with chenodeoxycholic acid (CDCA) and so prevent disease progression in the form of neurologic deterioration. We present 4 patients who had suffered neurologic symptoms since childhood and who were diagnosed with CTX after presenting with tendinous xanthomas.

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Table. Relevant Clinical Characteristics of the 4 Patients with Cerebrotendinous Xanthomatosis

Patient/ Sex	Neurologic Symptoms (Age at Onset, y)	Other Symptoms (Age at Onset, y)	Age at Onset of TX, y	Age at Diagnosis of CTX, y	Diagnostic Test and Results	Additional Tests	Treatment
1/F	Severe mental retardation Spastic paraparesis (5- 6)	Bilateral juvenile cataracts (5)	20	55	Cholesterol <4.4 mmol/L Urinary bile alcohols: 23,25 pentol: 11.681 mg/mol creat.; 24,25 pentol: 2.743 mg/mol creat.	EEG: abnormal basal activity of the δ waves BMRI: cerebral atrophy and hypodensity of cerebral hemispheres Echocardiogram: normal Echo-Doppler of supraaortic branches: normal	CDCA 750 mg/d Atorvastatin 40 mg/d (added later)
2/F	Mild mental retardation Learning difficulties, tremor, and ataxia (4)	Bilateral congenital cataracts Chronic diarrhea due to lactose intolerance (2)	18	26	Serum biochemistry: cholesterol: 5 mmol/L β -cholestanol: 99 μ mol/L	EEG: normal BMRI: normal Echocardiogram: normal Echo-Doppler of supraaortic branches: normal	CDCA 750 mg/d Atorvastatin 40 mg/d
3/M	Mild mental retardation Epilepsy (15)		30	32	Serum biochemistry: cholesterol: 4.9 mmol/L β -cholestanol: 87.6 μ mol/L	EEG: mild neuronal dysfunction BMRI: Minimal hypodensity of cerebral and cerebellar hemispheres Echocardiogram: Normal. Echo-Doppler of supraaortic branches: normal	CDCA 750 mg/d Simvastatin 20 mg/d
4/M	Epilepsy and schizophrenia (16) Behavioral disorder Suicide attempts (20)		30	33	Serum biochemistry: cholesterol: 4.8 mmol/L β -cholestanol: 122.6 μ mol/L	EEG: mild neuronal dysfunction BMRI: normal Echocardiogram: normal Echo-Doppler of supraaortic branches: normal	ACDCA 750 mg/d Atorvastatin 40 mg/d

Reference ranges: cholesterol < 6.1 mmol/L; β -cholestanol < 12 μ mol/L; 23,25 pentol < 5 mg/mol creatinine; 24,25 pentol < 23 mg/mol creatinine. Abbreviations: BMRI, brain magnetic resonance imaging; CDCA, chenodeoxycholic acid; creat., creatinine; CTX, cerebrotendinous xanthomatosis; EEG, electroencephalogram; F, female; M, male; TX, tendinous xanthomas.

Case Descriptions

Here we describe the cases of 4 patients who attended our department. Their ages ranged from 26 to 55 years and 2 were siblings (patients 3 and 4). The clinical characteristics of these patients are summarized in the Table. A description of patient 1 has been published previously.² The onset of symptoms, which were neurologic in all patients (mental retardation), occurred before the age of 20 years.

Two patients underwent cataract operations during childhood and 1 also suffered chronic diarrhea.

Skin lesions started to appear progressively 15 years after the onset of the neurologic symptoms, when the patients were teenagers or in their 20s. The lesions were solid, rounded, subcutaneous tumors of noninflammatory nature situated over the joints, with involvement of the Achilles, finger extensor, patellar, and triceps tendons (Figures 1 and 2). Some patients also presented xanthelasma. Histological study of these tumors showed a prolif-



Figure 1. Tendinous xanthomas in the Achilles tendons (patient 3).



Figure 2. Tendinous xanthomas in the extensor tendons of the fingers (patient 2).

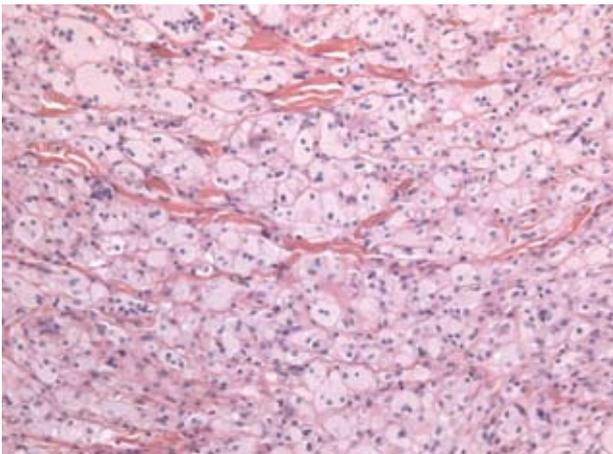


Figure 3. Histological appearance of a tendinous xanthoma (hematoxylin-eosin, $\times 100$) (patient 2) Xanthomatized cells separated by collagen bands.

eration of xanthomatous cells without atypia or mitoses. Abundant multinucleated Touton-like giant cells were observed and a mild interstitial inflammatory component accompanied by dermal collagen with hyalin degeneration was present. In some cases it was possible to discern biconvex fissures reflecting the shape of cholesterol crystals that dissolved while processing the biopsy specimen (Figure 3). These results were consistent with a diagnosis of tendinous xanthoma. In the neurologic examination of the patients, findings included isolated severe mental retardation, ataxic gait, amyotrophy of the limbs and generalized hyperreflexia, epilepsy, and psychiatric disorders such as behavioral disorders, and suicide attempts.

Faced with suspicion of CTX, serum β -cholestanol (patients 2, 3, and 4) and urinary bile alcohols (patient 1) were determined.

After confirmation of diagnosis, treatment was started with 750 mg/d of CDCA along with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. The abnormal biochemical findings quickly returned to normal and remained within normal range during follow-up; however, the neurologic symptoms remained almost unchanged and even worsened in some patients. Patient 3 died 4 years after diagnosis due to progressive neurologic deterioration and patient 1 was admitted to a geriatric residence and so was lost to follow-up.

Discussion

CTX is an inherited autosomal recessive disease classified within the group of normolipemic xanthomatoses.^{2,3} In addition to our 4 patients, 4 other cases have been published previously in Spanish journals, suggesting that CTX is a rare and perhaps underdiagnosed disease in Spain.⁷⁻⁹

Affected patients have a congenital deficiency of sterol-27 α -hydroxylase, a key enzyme in cholesterol metabolism. This deficiency causes deposition of its metabolites (β -cholestanol and bile alcohols) in tissues due to the lack of inhibitory feedback of CDCA.¹⁰ The gene responsible (*CYP27A1*) is located on the long arm of chromosome 2, where more than 50 different mutations have been identified.^{11,12} In most cases, an amino acid substitution is associated with an absence or an inactive form of the enzyme.⁵

The initial symptoms usually appear in the first 10 years of life, often in the form of cataracts.^{12,13} However, the disorder is not diagnosed in most patients until the full range of clinical symptoms have developed.¹⁴ Chronic

diarrhea that is difficult to control and that first appears during childhood is an uncommon symptom that is also attributed to CTX, but for some authors this is a key symptom for diagnosis.¹³ Accumulation of β -cholestanol in the brain and cerebrospinal fluid (CSF) is responsible for neurologic dysfunction. Given that many patients present with cerebral atrophy, it has been postulated that the elevated β -cholestanol levels in CSF could induce neuronal apoptosis.^{2,12}

Tendinous xanthomas, present in 90% to 95% of cases according to the series, are the characteristic cutaneous manifestation of the disease.^{13,14} These appear in individuals aged between 10 and 30 years old in the form of subcutaneous nodules located typically on Achilles tendons, and can also be present on the finger extensor, patellar, and triceps tendons.¹² Histological study reveals an aggregate of foamy cells separated by collagen bands, without atypia or mitoses.^{2,6,10} As was the case in our patients, recognition of tendinous xanthomas is essential for guiding the diagnosis of CTX in those individuals with neurologic disorders, cataracts, or chronic diarrhea of unidentified cause.

CTX is also characterized by a high incidence of associated coronary artery disease and aneurysms caused by premature atherosclerosis. Thus, screening for cardiovascular disease is recommended.¹² The patients die in their 30s or 40s as a result of progressive neurologic deterioration, pseudobulbar paralysis, or acute myocardial infarction.¹³

Diagnosis is confirmed by biochemical blood tests that include measurement of β -cholestanol, in parallel with an abnormal sterol profile characteristic of CTX, or by measurement of urinary bile alcohols by gas chromatography in tandem with mass spectrometry.¹⁰ Genetic study of family members can aid an early diagnosis in presymptomatic homozygotes and detect heterozygotes.^{5,15}

Treatment is based on administering the bile acids that are lacking. CDCA is used as standard therapy.¹ It appears that prolonged use could stop or, less likely, cause a regression of the disease, without any significant adverse effects.¹² Recent studies propose the addition of HMG-CoA reductase inhibitors (atorvastatin or simvastatin) because combination therapy with these drugs seems to lower cholesterol concentrations that increase with administration of CDCA.¹⁶⁻¹⁹ Neurological damage is irreversible. Treatment is only effective if initiated at the first sign of symptoms (cataracts, diarrhea, and mild neurologic abnormalities); when xanthomas have appeared it is usually too late to obtain satisfactory results. In our patients, treatment was started after the tendinous xanthomas had developed and so disease remission was not achieved, although progression was slowed in some cases.

Conclusion

CTX is a disease for which the keys to diagnosis are presence of neurologic symptoms, cataracts, or chronic diarrhea in young patients, and xanthomas from 10 years onwards. This disease has a specific treatment that is more effective the earlier it is started and that may sometimes improve the associated poor prognosis.

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Conflicts of Interest

The authors declare no conflicts of interest.

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