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Identification of Cerebrotendinous Xanthomatosis in High-Risk Children Using a Suspicion Index–Based Screening Strategy

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Abstract

Background

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid storage disorder that is amenable to disease-modifying therapy if diagnosed early. However, phenotypic heterogeneity frequently leads to delayed recognition, particularly in childhood.

Methods

We retrospectively screened pediatric patients with neurological and multisystem involvement using the Mignarri Suspicion Index (MI). Patients with MI ≥ 100 underwent biochemical and/or molecular evaluation for CTX.

Results

Of 65 high-risk children, CTX was confirmed in 3 (4.6%). All diagnosed patients had MI scores ≥ 100, but none exhibited the full classical triad. Median diagnostic delay was 7 years. Early initiation of chenodeoxycholic acid therapy led to biochemical normalization and clinical stabilization.

Conclusions

A suspicion index–based approach effectively identifies CTX among high-risk pediatric populations. Integrating MI screening with confirmatory testing may improve diagnostic pathways for rare but treatable neurometabolic disorders and reduce preventable morbidity.

Introduction

Cerebrotendinous xanthomatosis (CTX; OMIM #213700) is a rare autosomal recessive lipid storage disorder caused by biallelic pathogenic variants in the *CYP27A1* gene located on chromosome 2q35. The *CYP27A1* gene encodes mitochondrial sterol 27-hydroxylase, a key enzyme involved in bile acid biosynthesis. Deficiency of this enzyme leads to impaired bile acid synthesis and subsequent excessive accumulation of cholesterol and cholestanol in a wide range of tissues like the central nervous system, ocular lens, and tendons.(Nie et al. 2014; Nóbrega et al. 2022)

The disorder was first described by Van Bogaert in 1937, and since then, several hundred cases have been reported worldwide.(Nie et al. 2014; Nóbrega et al. 2022) However, the true prevalence of CTX is believed to be underestimated, with reported incidence rates varying considerably across ethnic groups and geographic regions. For example, incidence estimates range from 1:134,970 to 1:461,358 in

European populations, whereas markedly higher rates, up to 1:64,267, have been reported in East Asian populations.(Salen and Steiner 2017; Pramparo et al. 2023)

The clinical spectrum of CTX is highly heterogeneous. The disease may initially present during the neonatal period with prolonged cholestasis or refractory diarrhea, followed in childhood by manifestations such as juvenile cataracts, osteoporosis, and intellectual disability. In later stages, tendon xanthomas and a broad range of neurological manifestations—including myelopathy, ataxia, seizures, dementia, and psychiatric symptoms—may develop.(Berginer et al. 1984, 2009; Stelten et al. 2019) Substantial phenotypic variability is observed not only between unrelated patients but also among affected members of the same family, frequently resulting in delayed diagnosis.(Salen and Steiner 2017)

The diagnosis of CTX is established through a combination of suggestive clinical findings, elevated plasma cholestanol levels, and confirmation by *CYP27A1* genetic analysis.(Salen and Steiner 2017) Chenodeoxycholic acid (CDCA) therapy represents the cornerstone of treatment; when initiated at an early stage, it may prevent the development or progression of neurological manifestations, whereas its therapeutic benefit is considerably limited in later stages of the disease course.(Amador et al. 2018) Therefore, early recognition and timely initiation of treatment are critical to prevent irreversible neurological damage. To facilitate early diagnosis and support long-term disease management, a diagnostic tool known as the “Mignarri Suspicion Index” has been developed.(Mignarri et al. 2014)

In the present study, outpatient clinic records were retrospectively reviewed to identify previously undiagnosed or overlooked cases of CTX. The objectives were to characterize the initial clinical manifestations of these patients, to assess the discriminative value of the Mignarri Suspicion Index (MI) scores in the diagnosis of cerebrotendinous xanthomatosis, and to investigate the frequency of CTX among high-risk pediatric populations. By enabling diagnosis at the earliest possible stage and allowing prompt initiation of treatment, this approach aims to enhance clinical awareness of CTX and reduce diagnostic delay.

Materials and Methods

Patients followed at the Pediatric Neurology and Pediatric Metabolic Diseases outpatient clinics of Marmara University Faculty of Medicine between 2016 and 2022 were retrospectively reviewed. Suspicion of CTX was defined by the occurrence of one or more of the following clinical, radiological, or neurological manifestations: tendon xanthomas, congenital cataracts, chronic diarrhea, prolonged jaundice and/or cholestasis, ataxia and/or spastic paraparesis, intellectual disability and/or psychiatric manifestations, T2-weighted hyperintensities in the cerebellar dentate nuclei on magnetic resonance imaging (MRI), epilepsy, parkinsonism, and peripheral polyneuropathy.

All patients were evaluated using the Mignarri Suspicion Index (MI), and individuals with an MI score ≥ 100 were considered eligible for inclusion. A total of 65 patients meeting this criterion constituted the study cohort. In these patients, serum cholestanol concentrations were measured and/or *CYP27A1* mutation analysis was performed using next-generation sequencing techniques.

Only patients younger than 18 years at the time of initial clinical evaluation were included. Patients lacking molecular confirmation, those without regular clinical follow-up, or those with incomplete clinical or laboratory data were excluded from the analysis. Ethical approval for the study protocol was obtained from the local institutional review board (Ethical approval No. 1435, 03 December 2021).

Results

Demographic Characteristics

A total of 65 patients with an MI score ≥ 100 were included in the study. Of these, 31 patients (48%) were female and 34 (52%) were male. The mean MI score of the study cohort was 144.6 ± 40.1. Evaluation of MI parameter distribution revealed that the majority of patients exhibited one or more of the following clinical features: spastic paraparesis and/or ataxia, epilepsy, or intellectual disability.

The cohort had a mean age of 13.75 ± 5.33 years, with an age range from 3 months to 21 years and 4 months. Plasma cholestanol levels were measured by gas chromatography-mass spectrometry (GC-MS) in 27 patients whose samples were referred to a reference laboratory, as this assay was not routinely available at all centers. Plasma samples were saponified with potassium hydroxide, followed by lipid extraction with hexane and derivatization with BSTFA + TMCS, using 5α-cholestane as the internal standard.(AHMIDA 2006) Cholestanol levels above the laboratory reference threshold were considered suggestive of CTX and prompted confirmatory *CYP27A1* gene analysis. In the remaining 38 patients, diagnostic evaluation was performed by *CYP27A1* gene next-generation sequencing (NGS). Confirmatory genetic testing of the *CYP27A1* gene was performed by a pediatric metabolic specialist in all patients with cholestanol levels above the predefined threshold.

CTX was genetically confirmed in one female patient with elevated plasma cholestanol levels. Her male sibling, who had also been included in the study because of a high MI score, was subsequently diagnosed with CTX through genetic testing. In addition, one male patient received a direct molecular diagnosis. Consequently, 3 of the 65 patients (4.6%) were definitively diagnosed with CTX. The demographic characteristics of the study population are summarized in Table 1.

Table 1
Demographic characteristics of the patients

Gender	**Patients diagnosed with CTX (n = 3)**	**Patients diagnosed withot CTX (n = 62)**	**Total (n = 65)**
Male	2 (67)	32 (52)	34 (52)
Female	1 (33)	30 (48)	31 (48)
	Mean; median		
Age (year)			
Mean	15,33	10,78	10,99
Median (min, max)	15,29 (12,36 – 18,36)	10,69 (6,14–20,97)	10,94 (0,9–20,9)
Age at symptom onset (month)			
Mean	56	38,38	39,26
Median (range)	48 (48, 72)	15 (0,2-156)	16 (0,2-156)
	n (%)		
Initial symptom			
Xanthoma	1	0	1
Jaundice/cholestasis	0	5	5
Seizure	1	16	17
Intellectual disability	1	7	8
Gait disturbance	0	19	19
Cataract	0	2	2
Polyneuropathy	0	0	0
Other*	0	13	13
	Mean ± standard deviation		

(*Xanthoma, congenital cataract, chronic diarrhea, jaundice/cholestasis, ataxia and/or spastic paraparesis, intellectual disability and/or psychiatric disorder, T2 hyperintensity in the cerebellar dentate nuclei on magnetic resonance imaging (MRI), epilepsy, parkinsonism, and polyneuropathy; SD, standard deviation; ** p = 0.268.)

Gender	Patients diagnosed with CTX (n = 3)	Patients diagnosed withot CTX (n = 62)	Total (n = 65)	
Mignarri suspicion index (MI)	191,7 ± 80,4	142,34 ± 36,94	144,6 ± 40,1	*p > 0.05***
(*Xanthoma, congenital cataract, chronic diarrhea, jaundice/cholestasis, ataxia and/or spastic paraparesis, intellectual disability and/or psychiatric disorder, T2 hyperintensity in the cerebellar dentate nuclei on magnetic resonance imaging (MRI), epilepsy, parkinsonism, and polyneuropathy; SD, standard deviation; ** p = 0.268.)				

Characteristics of Patients with CTX

Among patients with MI scores ranging from 100 to 250, CTX was genetically confirmed in 3 individuals (4.6%). One of these diagnoses was established based on elevated plasma cholestanol levels, whereas the remaining two were identified through genetic analysis. The clinical and demographic characteristics, laboratory findings, and molecular results of patients with confirmed CTX are presented in Table 2.

Table 2
Clinical characteristics of CTX patients

Patient No	**1**	**2**	**3**
Gender	Male	Female	Male
Age at diagnosis (years)	11	15	9
Duration from initial symptoms to diagnosis (years)	7	11	3
Treatment	CDCA	CDCA	CDCA
Treatment duration (months)	50	36	36
Pre-treatment plasma cholestanol levels (mg/mL)	20	21.44	21.1
Post-treatment plasma cholestanol levels (mg/mL)	7,4 (Regular treatment for 10 months)	9,28 (Irregular treatment for 5 months)	7,7 (Regular treatment for 10 months)
Clinical features (age at onset)	Seizures (4 years) Cognitive decline (6 years) Learning difficulties (8 years) Cataract (10 years) Osteopenia (13 years)	Achilles tendon xanthoma (4 years) Learning difficulties (8 years) Cataract (16 years)	Intellectual disability (6 years)
Electrophysiological findings			
Electroencephalography (EEG)	Normal background activity; bilateral frontotemporal epileptiform discharges	Normal	Normal
Electromyography (EMG)	Normal nerve conduction	Normal nerve conduction	Normal nerve conduction
CYP27A1 gene variation	IVS7 + 4A > T (c.1263 + 4A > T) VUS	c.1_5delATGGC (p.M1Cfs*178)	c.1_5delATGGC (p.M1Cfs*178)
(VUS: Variant of uncertain significance)			

Patient 1 was a male patient who experienced his first epileptic seizure at 4 years of age. During follow-up, he developed epilepsy and spastic paraparesis and was diagnosed with cerebrotendinous xanthomatosis at the age of 11 years. His MI score was calculated as 225, corresponding to an

approximate diagnostic delay of 7 years. Genetic analysis revealed the *CYP27A1* IVS7 + 4A > T (c.1263 + 4A > T) variant, the clinical significance of which has not yet been clearly defined.

Patient 2 was a female patient whose initial clinical manifestation consisted of Achilles tendon xanthomas that appeared at 4 years of age (Fig. 1.). She underwent surgical intervention by the orthopedic department and had concomitant intellectual disability. A definitive diagnosis of CTX was established at the age of 15 years, and her MI score at diagnosis was markedly elevated.

Patient 3 was a male who had intellectual disability, and his MI score was calculated as 100. Genetic analysis of Patient 2 and 3, subsequently determined to be siblings, revealed the previously reported *CYP27A1* c.1_5delATGGC (p.Met1Cysfs*178) variant.

In all confirmed cases, *CYP27A1* variants were present in the homozygous state. Parental consanguinity was identified in both families in which CTX was diagnosed.

All patients with confirmed CTX were initiated on chenodeoxycholic acid (CDCA) therapy at at a dose of 10–15 mg/kg/day administered in two to three divided doses. The median diagnostic delay among patients with CTX was 84 months (range: 36–132 months).

In patients with a definitive CTX diagnosis, the only distinguishing clinical feature was the presence of Achilles tendon xanthomas, detected in a single patient. Comprehensive biochemical and genetic investigations were performed based on a high clinical suspicion index.

Discussion

Given the non-specific nature of its neurological manifestations, CTX may be misdiagnosed as hereditary spastic paraplegia, spinocerebellar ataxia, or multiple sclerosis and may present for years as an isolated, progressive gait disorder.(Koyama et al. 2021; O'Keefe et al. 2025) In contrast to many other causes of progressive ataxia or spastic paraparesis, however, CTX is a treatable disorder, and early initiation of chenodeoxycholic acid therapy may halt or reverse neurological deterioration.(Salen and Steiner 2017) Accordingly, cerebellar ataxia and spastic paraparesis are recognized as strong indicators in the Mignarri suspicion index.(Mignarri et al. 2014)

In this study, we examined the prevalence of CTX among high-risk pediatric patients with MI scores > 100 using plasma cholestanol measurement and genetic analysis. In the original study introducing the Mignarri Suspicion Index, all genetically confirmed CTX patients (100%) had MI scores ≥ 100 at diagnosis, with a median score of 300, and application of the index enabled diagnosis approximately 25 years earlier on average.(Mignarri et al. 2014) In another study screening 101 patients older than two years with autism spectrum disorder using the MI, CTX-associated *CYP27A1* variants were identified in four patients (3.9%).(Karadag et al. 2024) Similarly, in a cohort of 452 patients with idiopathic bilateral juvenile cataracts, CTX prevalence was calculated as 1.55%, based on the identification of biallelic pathogenic *CYP27A1* variants following detection of elevated cholestanol levels. However, the detection

of two CTX cases among individuals with MI scores < 100 suggests that the index alone may not be sufficient for diagnosis.(Atilla et al. 2021) Furthermore, published data indicate that the mean MI score at diagnosis is significantly lower in pediatric patients (267.8 ± 51.4) than in adults (450.0 ± 64.0; p = 0.001), highlighting age-related differences in clinical expression and diagnostic scoring.(Kısa et al. 2021)

In our cohort, CTX was identified in three children (4.6%), all of whom had MI scores ≥ 100 at diagnosis and were classified within the “strong suspicion” category. Nevertheless, the classical diagnostic triad—early-onset cataracts, tendon xanthomas, and progressive ataxia with pyramidal signs—was not fully present in any of our confirmed cases. These findings indicate that while the Mignarri Index demonstrates high diagnostic discriminative value in both adult and in pediatric populations, its combination with serum cholestanol measurement may represent a more sensitive and reliable screening approach for CTX.

In Patient 1, the *CYP27A1* c.1263 + 4A > T variant detected in our study represents a novel intronic change located near the splice donor site and has not been described in prior studies. Although in silico analyses suggest a potential impact on splicing, the absence of functional validation currently limits definitive classification, and the variant was therefore considered of uncertain significance (VUS) according to ACMG criteria.(Richards et al. 2015) Nonetheless, the clinical and biochemical findings were highly consistent with CTX, supporting the pathogenic relevance of this variant. Despite this, a diagnostic delay of approximately seven years was observed in this patient.

In the remaining two patients, the previously reported c.1_5delATGGC (p.M1Cfs*178) variant was identified. This early frameshift mutation affects the initiation codon and results in loss of function. Given that loss-of-function is the established disease mechanism for *CYP27A1*, This variant is classified as pathogenic based on ACMG criteria.(Richards et al. 2015) To date, more than 99 pathogenic *CYP27A1* mutations—including missense, nonsense, splice-site, and insertion/deletion variants—have been reported worldwide.(Salen and Steiner 2017) Although no consistent genotype–phenotype correlation has been established in CTX, substantial phenotypic variability has been described even among patients carrying identical genotypes.(Verrips et al. 2000; Pilo-de-la-Fuente et al. 2011; Stelten et al. 2019; Koyama et al. 2021) Nevertheless, a national study suggested possible associations between the c.1421G > A (p.R474Q) variant and classical CTX, the c.1214G > A (p.R405Q) variant and spinal-type CTX, and the c.435G > T (p.G145=) variant and CTX without neurological involvement.(Sekijima et al. 2018)

Neuroimaging studies have demonstrated that MRI is a fundamental tool for detecting diffuse or focal lesions in cerebral white matter and the cerebellum in CTX. Lesions involving the dentate nuclei and adjacent white matter are thought to reflect demyelination, necrosis, or cystic degeneration.(Hokezu et al. 1992; Berginer et al. 1994) Advanced neuroimaging techniques, including diffusion tensor imaging (DTI) and voxel-based morphometry (VBM), provide complementary information by enabling more detailed and comprehensive assessment of gray and white matter involvement.(Chang et al. 2010) However, no significant a relationship has been identified between severity of biochemical abnormalities

and MRI findings. In particular, serial MRI evaluations performed in 11 patients during CDCA treatment failed to show substantial changes, suggesting that MRI may have limited utility in monitoring treatment response.(Hokezu et al. 1992; Berginer et al. 1994)

In our study, no new or progressive cranial MRI abnormalities were observed either at diagnosis or during CDCA treatment. Moreover, no newly emerging neurological signs or symptoms occurred during follow-up. In the patient receiving antiepileptic therapy, no seizure recurrence was observed, and no adjustments to antiepileptic medication were required. Collectively, these findings support a neuroradiological course consistent with clinical stability.

Long-term oral chenodeoxycholic acid (CDCA) therapy is effective in correcting both biochemical abnormalities and clinical manifestations of CTX.(Salen et al. 1987; Samenuk and Koffman 2001; Berginer et al. 2009) When initiated during childhood, CDCA may halt disease progression and prevent neurological deterioration, whereas its therapeutic benefit is limited once irreversible neurological damage has occurred, with minimal clinical improvement in advanced disease.(Mignarri et al. 2012; Rubio-Agusti et al. 2012; Yahalom et al. 2013; Amador et al. 2018; Stelten et al. 2019) This narrow therapeutic window underscores the importance of early diagnosis; although CTX is considered an ideal candidate for newborn screening, it has not yet been incorporated into any national newborn screening program.(Hong et al. 2020; DeBarber and Duell 2021; Vaz et al. 2023) In the absence of universal screening, clinical suspicion remains essential; however, the Mignarri suspicion index relies on clinical and historical features, and its most heavily weighted findings, including tendon xanthomas, osteoporosis, and progressive neurological involvement, often emerge later in the disease course. Consequently, scores increase with age and are significantly lower in children than in adults, raising the possibility that pediatric patients with early or atypical disease may not reach the ≥ 100-point threshold and may therefore be missed by this screening approach.(Mignarri et al. 2014; Kısa et al. 2021)

The present study is particularly valuable in that it targets high-risk pediatric patients using the MI scoring system. Given the rarity of CTX, much of the existing literature is likewise based on limited case numbers. The main limitation of this study is the relatively small sample size. To determine the true prevalence of CTX in Türkiye, larger multicenter studies involving broader patient populations are warranted.

Conclusion

In conclusion, the combined use of the Mignarri Suspicion Index (MI), followed by serum cholestanol measurement and genetic mutation analysis, represents a reliable and efficient approach for the rapid identification of CTX in high-risk populations presenting with features such as spastic paraparesis/ataxia, intellectual disability, and cholestasis. The timing of diagnosis is of critical importance, as early initiation of chenodeoxycholic acid (CDCA) therapy has been shown to prevent the development of irreversible neurological damage. To further enhance awareness of CTX, improve

understanding of genotype–phenotype relationships, and assess long-term treatment outcomes, future studies involving larger and more diverse patient cohorts are strongly warranted.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Marmara university School of Medicine (Ethical approval No. 1435, 03 December 2021).

Consent to Participate

Written informed consent was obtained from the parents or legal guardians of the participants

Consent to Publish

Written informed consent for publication of the clinical image was obtained from the patient’s parent or legal guardian.

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Author Contribution

Author ContributionsSÖ conceived and designed the study. SÖ and İHA collected the clinical data and performed the clinical assessments. EYG and EG contributed to the biochemical and molecular investigations. SÖ, GAY, NEH, SK performed the data analysis and interpretation. SÖ drafted the manuscript. GÖ and OÜ critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures



Figure 1

Achilles tendon xanthoma observed in patient 2 at 15 years of age