



## Case Report

## Spinal cerebrotendinous xanthomatosis: A case report and literature review



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## ARTICLE INFO

## Keywords:

Cerebrotendinous xanthomatosis  
Spinal  
Medullar  
Clinical  
Chenodeoxycholic acid  
Genetic  
CTX

## ABSTRACT

**Background:** Classic cerebrotendinous xanthomatosis (CTX; OMIM #213700) manifests with chronic diarrhea, juvenile cataracts, tendon xanthomas and neurological symptoms. It is due to biallelic inactivation of *CYP27A1* which leads to cholestanol accumulation in the central nervous system, eyes and tendons. Less commonly, the disease can present in young adults as spastic paraparesis in the absence of xanthomas.

**Case presentation:** We report a 38-year old woman who presented with chronic diarrhea and progressive spastic paraparesis in her twenties. Brain magnetic resonance imaging (MRI) showed cerebral atrophy with diffuse periventricular white matter hyperintensities. Spinal MRI was normal. *CYP27A1* gene sequencing confirmed the diagnosis of CTX. Chenodeoxycholic acid (CDCA) treatment was introduced with remission of diarrhea. Unfortunately, the treatment had to be discontinued several times and the patient developed psychosis and an severe ataxospastic gait. Spinal MRI revealed new linear hyperintensities of the corticospinal and gracile tracts. Thirty-three spinal CTX patients were identified by searching in Pubmed, EMBASE™ and Web of Science databases. All patients presented pyramidal signs and 48% had dorsal column signs. Juvenile cataracts were described in 78% of patients, chronic diarrhea in 65%, and tendon xanthomas in 31%. Disease improvement or stabilization with chenodeoxycholic acid was observed in 69% of patients. A higher prevalence of the Arg395Cys allele was observed in patients with spinal CTX as compared to CTX in general ( $\chi^2$ ;  $p < 0.00001$ ).

**Conclusions:** The diagnosis of spinal CTX can be easily missed or delayed in absence of xanthomas. There is a higher prevalence of the Arg395Cys allele in spinal CTX as compared to classic childhood-onset CTX. CDCA treatment seems to stabilize or improve clinical symptoms in most patients. However, as seen in our patient and in two previously reported cases, sudden interruption of CDCA may lead to irreversible neurological complications.

## 1. Introduction

Cerebrotendinous xanthomatosis (CTX), OMIM #213700, is a rare autosomal recessive disorder of bile acid biosynthesis due to variants in the *CYP27A1* gene resulting in deficiency of sterol 27-hydroxylase (*CYP27A1*), a key-enzyme in the conversion of cholesterol to bile acids. The enzyme defect is responsible for a decrease in cholic acid (CA) and chenodeoxycholic acid (CDCA) biosynthesis. Due to the absence of CDCA negative feedback on 7- $\alpha$ -hydroxylase (*CYP7A1*), cholesterol is converted into cholestanol (dihydrocholesterol) [1,2], leading to high plasma levels of cholestanol, which then deposits in many tissues,

especially in the lens, the muscle tendons and the central nervous system. CTX is slowly progressive and variable presentation, with symptoms and signs increasing with age in untreated patients. The prevalence of CTX is estimated to be 3 to 5 per 100,000 [3,4] but is probably underestimated. The classic form is characterized by infantile-onset diarrhea, premature bilateral cataracts, developmental delay with or without epilepsy, adolescent to young adult-onset tendon xanthomas and adult-onset progressive neurologic dysfunction which typically includes intellectual disability, progressive cerebellar ataxia and pyramidal signs (which become evident in the second or third decade), sensory-motor neuropathy, pseudobulbar symptoms (such as dysarthria and

**Abbreviations:** MRI, Magnetic resonance imaging; CA, Cholic acid; CDCA, Chenodeoxycholic acid; CTX, Cerebrotendinous xanthomatosis; ENMG, Electromyography; IQR, Interquartile range; BBB, Blood-brain-barrier.

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<https://doi.org/10.1016/j.ymgmr.2021.100719>

Received 4 December 2020; Received in revised form 22 January 2021; Accepted 22 January 2021

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dysphagia) and dementia.

The biochemical abnormalities that distinguish CTX from other conditions with xanthomas include high plasma and tissue cholestanol concentration, increased plasma cholestanol/cholesterol ratio [5], decreased CDCA, increased concentration of bile alcohols and their glycoconjugates in plasma and urine.

Brain MRI may reveal cerebral and cerebellar atrophy. Findings that are more specific are bilateral hyperintensities of the dentate nuclei, cerebral and cerebellar white matter [6]. Treatment with CDCA can improve symptoms of CTX by direct inhibition of CYP7A1 and negative feedback on cholesterol biosynthesis, thereby reducing accumulation of toxic metabolites [7,8]. Combination of CDCA with inhibitors of HMG-CoA reductase further reduce cholestanol levels and improves clinical signs [9].

Some CTX patients escape the pediatric presentation and develop, as young adults, a progressive spastic paraparesis as the main symptom. This form, so-called “spinal xanthomatosis”, is considered a clinical and radiological variant of CTX. The biochemical profile is the same. Spinal MRI typically shows abnormal linear T2 signal hyperintensities in the lateral corticospinal and gracile tracts.

Given the rarity of this condition, we report the case of a late-diagnosed patient with CTX who developed, after treatment discontinuation, a psychiatric disease and a marked spinal xanthomatosis. We also reviewed 33 cases of patients with a spinal CTX from the literature to gather further insight into the phenotype, genotype and clinical outcome of spinal xanthomatosis.

## 2. Case presentation

A 38-year-old woman presented with progressive muscle stiffness, calf cramps and urinary frequency appeared in her twenties (Fig. 1). Her past medical history included chronic diarrhea, scoliosis and bilateral cataract surgery at age 25. She did not take any treatment and had normal schooling. Family history was not relevant. Neurological examination revealed spastic paraparesis with pyramidal signs more prominent on the left lower extremity and flat feet. A neurocognitive study demonstrated severe anterograde verbal memory difficulties and minor executive dysfunction. Electroneuromyography (ENMG) was normal. Brain MRI showed subtle symmetric, bilateral hyperintense T2 ground-glass appearance of the deep white matter, possible symmetric T2 hyperintensity of the cerebellar dentate nuclei and two small ischemic infarct sequelae of the right cerebellar hemisphere (Fig. 2). Spinal MRI was normal. 7 years later, due to progression of spastic paraparesis, CTX was considered. Cholestanol was increased to 64  $\mu\text{mol/L}$  (3.3–12.5  $\mu\text{mol/L}$ ). A careful assessment did not find any tendinous

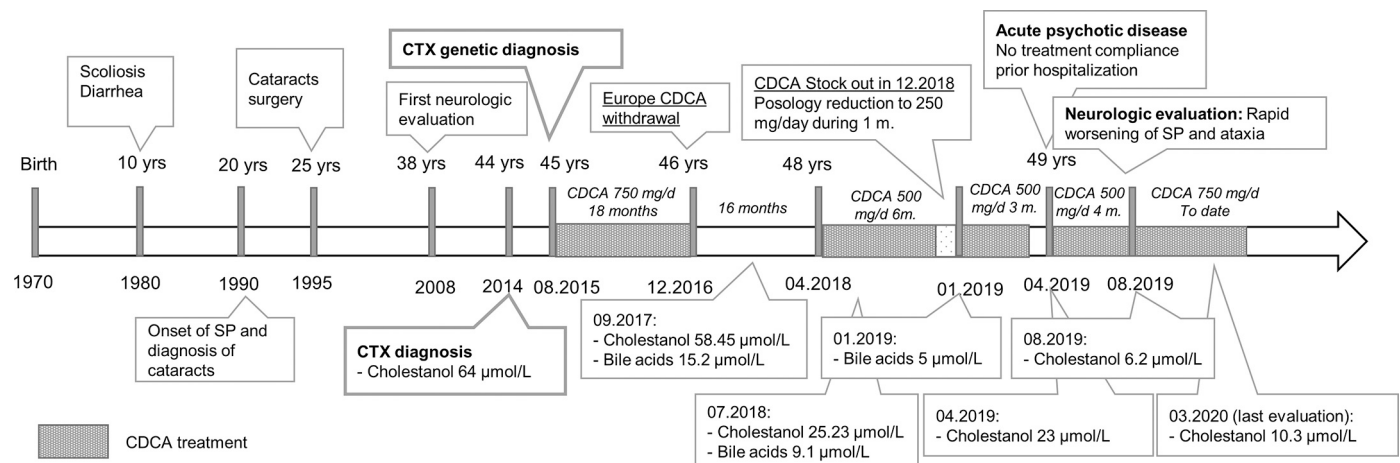
xanthomas. Genetic analysis found two monoallelic mutations in the gene *CYP27A1*: a missense mutation (c.1183C > T; p. Arg395Cys) in exon 6 and a splicing mutation (c.1184 + 1G > A) in intron 6 and confirmed CTX diagnosis. A treatment with 750 mg/d chenodeoxycholic acid (CDCA) and 20 mg/d simvastatine was introduced (Fig. 1). Three months later, diarrhea was disappeared and no adverse effect was observed. One-year follow-up showed stabilization of neurologic and radiologic signs.

CDCA treatment was stopped for 16 months due to product withdrawal. Over this period, diarrhea recurred and walking worsened. She had increased stiffness with muscle pain, new apallesthesia of the lower limbs and onset of cerebellar ataxia. When CDCA treatment was reintroduced (500 mg/d) walking, pain and diarrhea improved. Due to renewed product shortage and patient non-compliance, CDCA treatment was repeatedly discontinued, following which the patient developed an acute psychosis and, short after, a rapid worsening of her gait becoming rollator dependent. Neurologic evaluation showed a severe ataxospastic gait with knee recurvatum (additional files: video). ENMG was normal. Brain MRI was unchanged. Spinal MRI revealed extensive linear T2 weighted hyperintensities appearing bilaterally in lateral corticospinal and gracile tracts (Fig. 2). Despite normal cholestanol levels (6.18  $\mu\text{mol/L}$ ; normal range 3.3–12.5  $\mu\text{mol/L}$ ), CDCA posology was increased to 750 mg/d. Six months later, the patient had resolution of diarrhea and psychiatric symptoms but no improvement of gait.

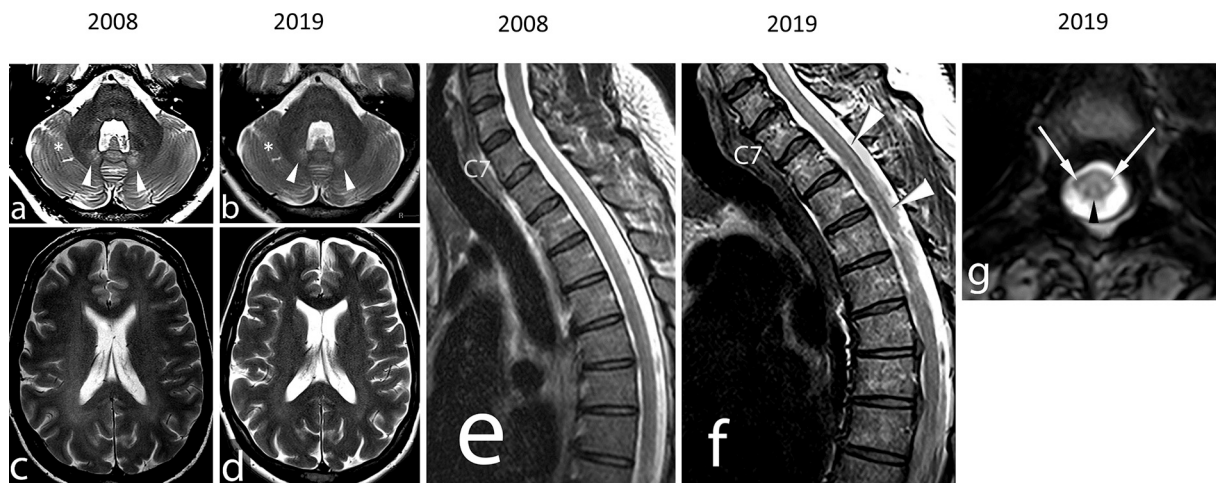
## 3. Material and methods

### 3.1. Literature review and analysis on spinal form of CTX

We searched Pubmed, EMBASE™ and Web of Science databases using “spinal and xanthomatosis”, “spinal and xanthoma” “spinal and cerebrotendinous xanthomatosis”, “medullar and xanthomatosis”, “medullar and xanthoma” and “medullar and cerebrotendinous xanthomatosis” as keywords. Patients with isolated spinal xanthomas or without biochemically and/or molecularly confirmed diagnosis of cerebrotendinous xanthomatosis were excluded. Only patients with clinical features of spinal CTX and/or with a typical spinal MRI were further evaluated. Additional studies of interest were identified by hand searches of bibliographies. Full text articles in English, French or Spanish with abstract in English were included. Four abstracts were included. The search was last updated on 28th April 2020. When needed, cholestanol units were converted into  $\mu\text{mol/L}$ . In order to avoid confusion, nucleotide and amino acid numbering are in both new nomenclature [10] and old nomenclature, in bracket [11]. Descriptive statistical analysis was performed with SPSS 25. Results are presented, including patient number (n) and frequency (%),



**Fig. 1.** Patient timeline of clinical symptoms and biochemical values. Abbreviations: SP: spastic paraparesis; m: month; CDCA: chenodeoxycholic acid. Normal values for cholestanol (N: 0–15.45  $\mu\text{mol/L}$ ); bile acid (N: 0–10.02  $\mu\text{mol/L}$ )



**Fig. 2.** Brain and spinal cord magnetic resonance imaging (MRI) of the patient. Brain and spinal cord MRI performed in 2008 (a,b,e) and 2019 (c,d,f,g). Axial plane T2 weighted images (a-d) at the level of the dentate nuclei and periventricular white matter showing stable minimal increased signal in the dentate nuclei (arrowheads) and questionable slightly abnormal periventricular white matter T2 hyperintensity (“ground-glass appearance”). The rest of brain MRI was unremarkable except for two small old infarcts in the right cerebellar hemisphere (one lesion shown in a and b\*). Spinal cord MRI from 2008 (e) was unremarkable, though no axial plane images were performed. Spinal cord MRI in 2019 revealed subtle longitudinal high signal (white arrow-heads) of the posterior columns at the cervico-dorsal junction and middle dorsal region on sagittal T2-weighted images (f). Axial T2-weighted images confirmed bilateral, symmetric signal abnormalities corresponding to the gracilis tracts (g, black arrowhead) and the lateral cortico-spinal tracts (g, white arrows) at different cervical and dorsal levels, without spinal cord atrophy or contrast material (gadolinium) uptake.

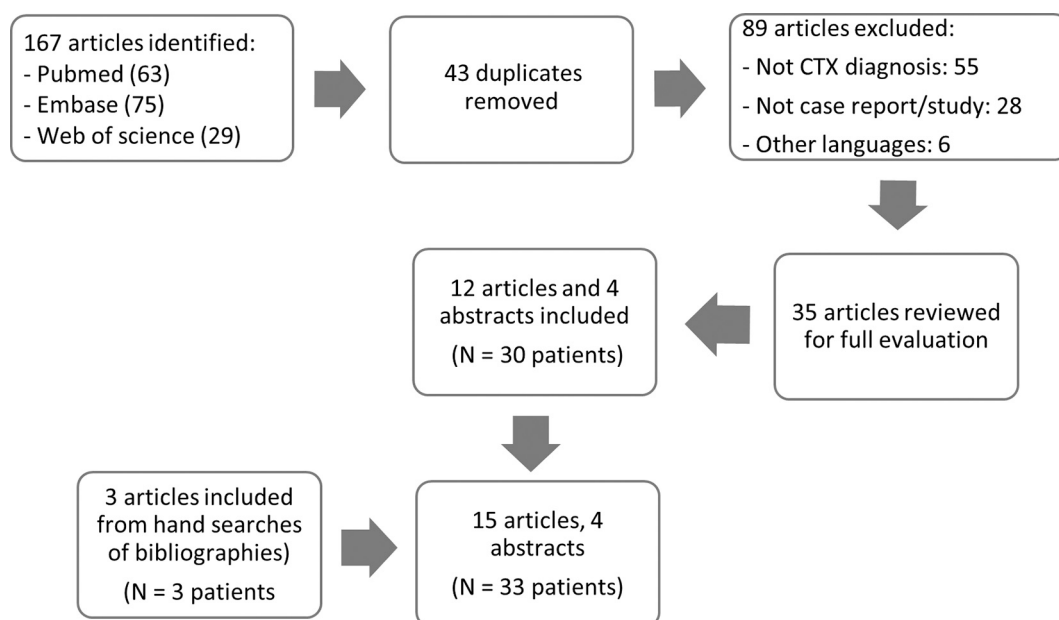
median and interquartile range (IQR Q25-Q75). Group comparison of categorical variables were performed using the Chi-squared test. Significance was set at  $p < 0.05$ .

#### 4. Results

Results of database searches are summarized in Fig. 3. Individual characteristics are described in Table 1. The main clinical and radiological features are outlined in Table 2. Fourteen patients were females and 11 males ( $n = 25$ ; sex data was not available for 8 patients) with a median age of 36 years (IQR 30–46 yrs.) ( $n = 32$ ). Median age to onset of neurological symptoms was 24 years (IQR 12–30 yrs.) ( $n = 31$ ). Only 2 patients (6%;  $n = 33$ ) presented with the classic triad of CTX signs.

Biochemical parameters were reported in 23 cases. All patients showed high plasma cholestanol levels (median levels of  $63 \mu\text{mol/L}$ ; IQR  $30\text{--}89 \mu\text{mol/L}$ ; N:  $2\text{--}12 \mu\text{mol/L}$ ).

In untreated patients the disease progressed slowly, though in 2 cases the disease was more aggressive leading to wheelchair dependent patients at the age of 30 years and 35 years, respectively. All patients received CDCA together with inhibitors of HMG-CoA reductase (pravastatin, simvastatin or atorvastatin) in 8 patients, vitamin E in 6 patients and vitamin D in 1 patient. One patient interrupted CDCA treatment due to probable drug-induced liver injury. When described, improvement was observed in bowel function, psychiatric disease, cognitive and motor function with reduction of spasticity. Improvement in ENMG and brain and spinal MRI were observed in one



**Fig. 3.** Results of literature search. Flow diagram demonstrates the review and selection process for published articles and abstracts to identify patients with clinical features of spinal form of cerebrotendinous xanthomatosis.

**Table 1**  
Clinical, radiological and molecular data of 33 patients with spinal CTX reported in the literature and our case report.

ID	Sex	Country origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. $\mu\text{mol/l}$ (2–12)	Brain MRI	Medullar MRI	Treatment Per day	Disease Evolution	Genetic variant	Ref
1	M	Spain	31	34	+	-	+	+	+		89	Parieto-occipital and CWML	Anterior and posterior cervical and dorsal SCWML	CDCA 750 mg	At 42 m.: symptom stabilization, mild ENMG improvement, vanishing cerebellar and medullar WML.	NA	[12]
2	F	Netherlands	20	23	-	+	+	+	+	Epilepsy	61	CWML	Lateral and dorsal SCWML	NA	NA	p.Thr306Met / p.Thr306Met	[6]
3	F	Netherlands	24	45	-	+	+	+	+	Dysarthria, cerebellar signs	19	NA	NA	NA	NA	p.Thr306Met / p.Arg395Cys	[6]
4	M	Netherlands	30	33	+	-	+	+	+		NA	CWML	Lateral and dorsal SCWML	NA	NA	p.Thr306Met / p.Arg395Cys	[6]
5	M	Netherlands	35	43	-	-	+	+	+	Dysarthria, cerebellar signs, polyneuropathy	NA	CWML	Lateral and dorsal SCWML	NA	NA	p.Arg94Trp / p.Thr306Met	[6]
6	F	Netherlands	35	37	-	-	+	+	+		46	CWML	NA	NA	NA	p.Thr306Met / p.Thr306Met	[6]
7	F	Netherlands	28	41	-	+	+	+	+		63	Normal	Lateral and dorsal SCWML	NA	NA	p.Thr306Met / c.1284 + 1G > A	[6]
8	F	Netherlands	28	36	-	+	+	+	+	Dementia	100	CWML	Lateral and dorsal SCWML	NA	NA	p.Arg395Cys / 865 + 1G	[6]
9	M	Spain	11	27	-	NA	+	+	NA	Seizures	60	Hypersignal dentate nuclei	Normal	NA	NA	NA	[13]
10	M	Spain	12	27	-	NA	+	+	NA	Seizures, myoclonia	90	Cerebral atrophy, hypersignal dentate nuclei	Normal	NA	NA	NA	[13]
11	F	Switzerland	25	51	-	+	+	+	NA	Behavior troubles, cognitive decline, depression	139	CWML, periventricular WML and dentate nuclei	NA	CDCA	NA	p.Ala216Pro / p.Arg405Trp	[14]
12	F	Switzerland	25	52	-	-	-	+	+		69	Normal	NA	CDCA	NA	p.Ala216Pro / p.Arg405Trp	[14]
13	M	German	16	44	NA	NA	+	+	NA	Dementia, seizures	61 (4.9 mg/dL)	Cerebellar and dentate nuclei gliosis	NA	CDCA 1 g + simvastatin	At 10 months; stabilization	NA	[15]
14	M	Chili	34	39	+	+	+	+	+	Dementia, psychiatric disease, urinary incontinence	NA	Hyperintensities dentate nuclei and CWML	Posterior SCWML	CDCA 750 mg	Improvement. At 8 m: autonomous, walking alone, and psychiatric symptoms.	NA	[16]
15	NA	Spain	10	30	-	NA*	NA*	+	NA	Ataxia, seizures, neuropathy, psychiatric disease	66	Normal	NA	CDCA + Vit. E + pravastatin	Progression	p.Gln230Ter / p.Arg395Cys	[17]
16	NA	Spain	12	23	-	NA*	+	+	NA	Ataxia, neuropathy, psychiatric disease	63	Normal	NA	CDCA + Vit. E + pravastatin	Progression	p.Gln230Ter / p.Arg395Cys	[17]
17	NA	Spain	18	32	-	NA*	NA*	+	NA	Seizures, ataxia, psychiatric disease	119	Atrophy demyelination	NA	CDCA + Vit. E + atorvastatin	Stabilization	c.844 + 1G > T / p.Arg395Cys	[17]
18	NA	Spain	20	36	-	NA*	NA*	+	NA	Psychiatric disease	NA	Atrophy, leukoaraiosis	NA	CDCA + simvastatin	Progression	p.Arg395Cys / p.Arg395Cys	[17]
19	NA	Spain	30	32	+	NA*	NA*	+	NA	Psychiatric disease	NA	Normal	NA	CDCA + vit. E	Stabilization		[17]

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Table 1 (continued)

ID	Sex	Country origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. $\mu\text{mol/l}$ (2–12)	Brain MRI	Medullar MRI	Treatment Per day	Disease Evolution	Genetic variant	Ref
20	NA	Spain	12	46	-	NA*	NA*	+	NA	ID, neuropathy, psychiatric disease	NA	Atrophy	NA	CDCA + vit. E pravastatin	Stabilization	p.Arg395Cys / p.Arg395Cys / c.1414–1421 del-GGGGTCCG	[17]
21	NA	Spain	12	46	+	NA*	NA*	+	NA	ID, neuropathy, psychiatric disease	NA	Atrophy	NA	CDCA + statin + vit. E	Progression	p.Arg395Cys / c.1414–1421 del-GGGGTCCG	[17]
22	F		Child	30	+	NA	+	+	+	Truncal ataxia	NA	Increased signal in basal ganglia, dentate nucleus, pons, medulla oblongata	Increased posterior and lateral SCWML	NA	NA	NA	[18]
ID	Sex	Country Origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. $\mu\text{mol/l}$ (2–12)	Brain MRI	Medullar MRI	Treatment Per day	Disease Evolution	Genetic variant	Ref
23	M	UK	24	27	-	+	-	+	NA	Urinary frequency, depression	112	Normal	Normal	NA	NA	p.Arg395Cys / p.Arg395Cys	[19]
24	M	Japan	39	46	-	NA	-	+	+		30 (24.1 $\mu\text{g/mL}$ )	CWML	Lateral corticospinal and gracile tracts hyperintensities	CDCA 750 mg discontinued + atorvastatine	NA	p.Arg405Gln / p.Arg405Gln	[20]
25	F	Chili	28	31	-	+	+	+	+	Cerebellar sd. At 42 y: severe spastic tetraparesis, flexum of the 4 limbs, severe dysphagia.	64	Involutive cerebellar and frontal regions, bulbar and CWML	NA	NA	NA	p.Val86Glnfs30Ter / p.Arg395Cys	[21]
26	M	Japan	65	77	+	+	-	+	NA		13 (10.4 $\mu\text{g/mL}$ )	Normal	Cervical dorsal column hyperintensities	CDCA 750 mg	NA	p.Gln85Arg / p.Arg405Gln	[22]
27	F	NA	5	52	-	NA	+	+	NA	Seizures, development delay, dystonia, ataxia, dysarthria, dysphagia, wheelchair at 30y., bedridden at 49 y.	19.6	Cerebral and CWML and atrophy, extensive, symmetric supra and infra-tentorial hyperintensities	Central and posterior SCWM, C7 through thoracic vertebra	NA	NA	Confirmed by genetic analysis. Exact mutation NA	[23]
28	M	China	18	36	+	-	+	+	+	Cognitive decline, walker at 30 y. and wheelchair at 35 y.	43 (34.8 mg/L)	Hypersignal internal capsule, brain peduncles, pontine median raphe, cerebellar peduncles, medullar pyramids. Global atrophy.	Longitudinal lateral funiculi and corticospinal SCWML of cervical and thoracic spine.	CDCA 500 mg increased to 750 mg	At 6 m.: improved spasticity and walk few steps by walker. At 8 m.: improved cognitive and cerebellar function. At 2.5 y.: improved cognition, strength and xanthomas size. Stabilization	Homozygous carrier of a late nonsense mutation. Exact mutation NA.	[24]
29	NA	NA	NA	NA	+	+	-	+	NA	Seizures	NA	Hypersignal dentate nuclei, diffuse cerebral and cerebellar atrophy		CDCA		NA	[25]
30	F	Caucasso	16	56	+	+	+	+	NA	Ataxia, behavioral, dysarthria, cognitive	23 (1.81 mg/dL)	Diffuse cerebral and CWML	SCWML	NA	NA	NA	[26]

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Table 1 (continued)

ID	Sex	Country Origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. $\mu\text{mol/l}$ (2–12)	Brain MRI	Medullar MRI	Treatment Per day	Disease Evolution	Genetic variant	Ref
31	F	Turkey	32	52	-	-	-	+	+	impairment, learning difficulties	n: <0.248) 19 (15 $\mu\text{g}/\text{mL}$ )	Bilateral symmetrical internal capsule, crus cerebri, and dentate nuclei lesions	Longitudinal SCWML	CDCA	NA	p.Leu524Arg / p.Leu524Arg	[27]
32	F	Chili	22	22	-	+	+	+	NA		NA	CWML and dentate nuclei	Lateral and dorsal SCWML	CDCA + vit D	NA	p.Arg395Cys / p.Arg395Cys	[28]
33	F	Caucasso	5	28	-	+	+	+	+	Neurocognitive regression, cerebellar signs, dementia	78 (6.24 $\text{mg}/\text{dL}$ )	CWML, cerebral and cerebellar atrophy	Lateral and dorsal SCWML	CDCA 750 mg	1 y.: cognitive improvement, normal bowel function, falls reduction.	p.(Lys284Leufs*3) / p.(Lys284Leufs*3)	[29]
34	F	Switzerland	20	38	-	+	+	+	+	Cerebellar signs, psychiatric disease	64	Periventricular WML	Linear hyperintensities	CDCA 500 mg increased to 750 mg	Diarrhea and neurologic improvement with CDCA; psychiatric disease and spinal CTX when interrupted	p.Arg395Cys / c.1184 + 1G > A	NA <sup><math>\beta</math></sup>

Patient 10 / 11, 12 /13, and 21 /22 were brothers / sisters. \*In Pilo de la Fuente cohort cataracts were present in 92%, tendon xanthomas in 56% and chronic diarrhea in 92% of patients. Mutations in bold have not been previously described in patients with classic CTX.  <sup>$\beta$</sup>  ID 34 is the described case report (not included in the statistics).

Abbreviations: X: xanthomas; C: cataracts; D: diarrhea; +: present; -: absent; NA: not available; PS: pyramidal signs; DCS: dorsal column signs; ID: Intellectual disability; dx: diagnosis; m: months; y: years; CWML: cerebellar white matter lesions; SCWML: spinal cord white matter lesions; WML: white matter lesions; ENMG: electroneuromyography; CDCA: chenodeoxycholic acid; vit: vitamin.



**Table 2**  
Main clinical and radiological features of patients with spinal cerebrotendinous xanthomatosis.

Clinical Features	Number of patients	%	N
Pyramidal syndrome	33	100%	33
Cataracts	21	78%	27
Chronic diarrhea	13	65%	20
Dorsal column signs	16	48%	33
Xanthomas	10	31%	32
Psychiatric symptoms	11	33%	33
Cerebellar signs	10	30%	33
Seizures	6	18%	33
Polyneuropathy	6	18%	33
Dementia or cognitive decline	6	18%	33
Intellectual deficiency	4	12%	33
Dysarthria	4	12%	33
Urinary troubles	2	6%	33
Dysphagia	2	6%	33
<b>Radiological features</b>			
Cerebral MRI:			31
- White matter lesions	16	48%	
- Hypersignal dentate nuclei	9	27%	
- Cerebral atrophy	10	30%	
Spinal cord MRI:			19
- Linear hyperintensities lateral and posterior cortical tracts	16	84%	
<b>Disease outcome with CDCA treatment</b>			13
- Disease improvement			
- Disease stabilization	4	31%	
- Disease progression	5	38%	
	4	31%	

patient with subclinical neuropathy after 42 months of CDCA treatment.

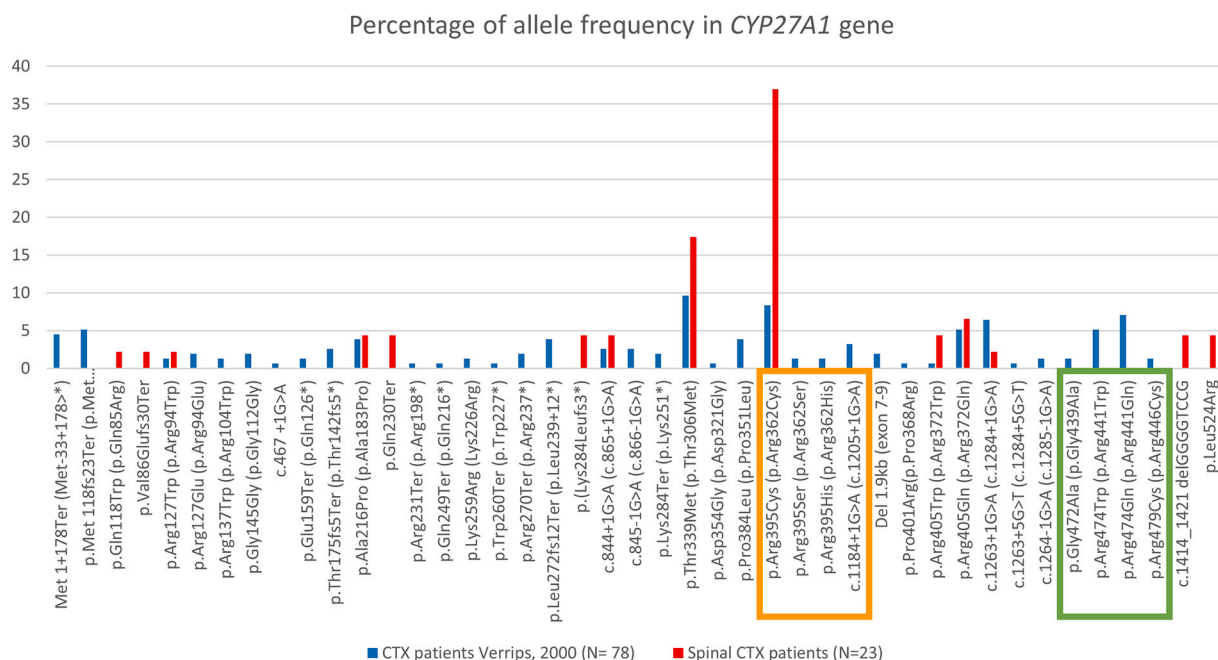
Results of genetic analysis were available for 23 patients. Allele frequencies are represented in Fig. 4. The two most frequent *CYP27A1* variants observed in spinal CTX patients were Arg395Cys and Thr339Met, with an allele frequency of 17/ 46 (36%) and 8/46 (17%), respectively. We observed a statistically significant higher frequency of

the *CYP27A1* allele p.Arg395Cys (p.Arg362Cys in old nomenclature) in patients with spinal CTX than in a general cohort of CTX patients described by Verrips et al. [30] (13/156; 8%) ( $\chi^2 = 23.02$ ;  $p < 0.00001$ ). In contrast, no difference was found for the Trp339Met allele ( $\chi^2 = 2.47$ ;  $p = 0.12$ ; allele frequency in the cohort from Verrips et al. 9.6%; 15/156). Reanalysis of another previously reported cohort of 24 CTX patients (17 with classic and 7 with spinal CTX; 48 alleles) [17], also showed a higher frequency of the p.Arg395Cys allele in the spinal CTX group (spinal CTX 9/14; 64%; classic CTX, 8/34; 23%).

## 5. Discussion

Since the description of CTX in 1937 [31], more than 300 patients have been described worldwide. The classic form of CTX is the most frequent clinical presentation. However, clinical presentation can be variable in type, severity, and timing even in identical twins [17,30]. In some cases, spastic paraparesis is the sole symptom of the disease for many years leading to CTX misdiagnosis. Absence of tendon xanthomas reported in 69% of the patients might partially explain the long diagnostic delay of about 10 years observed in spinal CTX patients (as in our case). Thus, both classical and spinal CTX are currently under-diagnosed [32]. Improvement of patient screening strategies are needed as early intervention prevents disease progression. Pediatricians and ophthalmologists play key roles in CTX diagnosis as neonatal diarrhea and juvenile cataracts are frequently the first symptoms observed in CTX. Prevalence of CTX in patients with bilateral juvenile-onset cataracts is estimated to 1.8% - 4% [33,34]. When present, tendinous xanthomas, although also found in familial hypercholesterolemia and sitosterolemia, might be an important diagnostic clue for dermatologists. However, the "CTX suspicion index" developed by Mignarri et al. [35] emphasizes the importance of cataracts and diarrhea (rather than xanthomas) in CTX diagnosis.

In spinal CTX patients, the first neurological signs were spastic paraparesis with stiffness, hyperreflexia and positive Babinski signs, associated with proprioceptive symptoms in approximately half of the cases. About one third of spinal CTX patients developed psychiatric disturbances. However, most of the patient did not present developmental



**Fig. 4.** Percentage of allele frequency in *CYP27A1* gene. Mutations distribution in percentage in 78 patients CTX patients from the paper of Verrips et al. 2000 (in blue) [30] and from all spinal CTX patients described in Table 1 ( $n = 23$ , in red). Nucleotide and amino acid numbering are in new nomenclature [10] and in bracket in old nomenclature [51].Ter (new nomenclature) and \* (old nomenclature): premature stop codon. Framed in orange, the mutations found within the adrenodoxin binding site (residues 351–365 old nomenclature) and framed in green mutation found within the heme binding site (residues 435–464 old nomenclature).

delay nor intellectual deficiency, which are frequent in the juvenile form of CTX. Linear hyperintensities of the lateral and posterior cortical tracts in spinal MRI was observed in most spinal CTX patients. Asymptomatic or paucisymptomatic spinal involvement of classical CTX is not known, as spinal MRI is not routinely performed. Although most of the neurological features are due to cholestanol accumulation on the frontal cortex, the cerebellum and spinal cord [6,36,37], the mechanism by which cholestanol accumulates in the central nervous system (CNS) is not fully understood. It seems that cholestanol itself does not efficiently cross the intact blood-barrier-barrier (BBB) and that the bile acid precursor  $7\alpha$ -hydroxy-4cholesten-3-one, which passes the BBB at a markedly higher rate (100 folds) [38], can be efficiently converted to cholestanol by neurons, astrocytes and microglia leading to cholestanol accumulation [38,39]. However, the efficiency of  $7\alpha$ -hydroxy-4cholesten-3-one conversion into cholestanol is not the same for all cell types [38]. Whether this observation, together with CYP27A1 residual enzyme activity, could contribute to the different phenotypes observed in CTX patients remains to be determined. The timing of CDCA introduction has a significant role in the outcomes of CTX patients. Early CDCA treatment is able to reverse neurological symptoms [40] or even prevent CTX features, in asymptomatic patients [41] and has a positive impact on disease evolution and/or symptoms in most spinal CTX patients described in this study. However, CDCA seemed to have a limited impact on the spinal cord syndrome. Because CDCA treatment might prevent a severe form of CTX and there is a reliable screening test ( $7\alpha,12\alpha$ -dihydroxy-4-cholesten-3-one quantification on dried bloodspot samples) [42], CTX should be considered for newborn screening. Thus, the population incidence of CTX is comparable to that of other disorders screened [43,44]. This strategy would prevent late or incorrect diagnosis, minimize unnecessary health expenditures and allow providing prompt genetic counselling.

Our patient showed improvement of her chronic diarrhea and stabilization of neurological symptoms under CDCA treatment. After treatment was discontinued several times because of product stock out and withdrawal from the market, the patient developed cerebellar ataxia, neuropathy, psychiatric symptoms and a severe ataxospastic gait. Noteworthy, Luyckx et al. described 2 brothers with stable CTX, treated with CDCA and statins during 11 years, who developed pyramidal signs and speech disturbances when CDCA treatment was discontinued because of product withdrawal [45]. The three cases suggest that abrupt interruption of CDCA may lead to rapid disease progression. This could be due to acute increase of circulating bile alcohol glucuronides, disrupting the BBB, [46,47] and/or increase levels of  $7\alpha$ -hydroxy-4cholesten-3-one, which would effectively cross the BBB and be transform into cholestanol. In untreated CTX patients an unusual increase activity of CYP8B1 (80%) was observed [48] which is able to transform  $7\alpha$ -hydroxy-4cholesten-3-one into  $7\alpha,12\alpha$ -dihydroxy-4-cholesten-3-one. As CYP8B1 activity is reduced by CDCA [49], it is possible that for a transient period of time after CDCA interruption patient are exposed to higher levels of  $7\alpha$ -hydroxy-4cholesten-3-one due to the absence of the CYP8B1 compensatory activity leading to brain and spinal cholestanol accumulation. Although further studies need to be perform to confirm or refute this hypothesis, clinicians and patients need to be aware of the possible consequences of interrupting CDCA treatment. It would be useful if international drug authorities might refine current policies with pharmaceutical companies to guarantee drug access, market availability and affordability of orphan drugs in order to avoid treatment discontinuation.

To date, there are 70 confirmed pathogenic variants causing CTX and 39 likely pathogenic variants in CYP27A1 [50]. No clear genotype-phenotype correlation has been observed. We observed a high frequency of the p.Arg395Cys allele in spinal CTX patients, although this variant was also frequently observed in classic CTX. The p.Arg395Cys substitution affects a highly conserved sequence of the adrenodoxin binding site and was shown to strongly reduce CYP27A1 enzyme activity [51]. Tridimensional protein modelling showed that Arg395 is located within the ERR triad (the glutamine-arginine-arginine motif conserved in all cytochrome P450

sequence) and its substitution to cysteine was suggested to favour misfolding and possibly affects adrenodoxin binding [21].

In summary, our review of the literature highlighted features of spinal CTX (as opposed to classic CTX) such as later age at presentation (early adulthood vs pediatric age), absence of xanthomas in two-thirds of patients and absence of development delay and intellectual disability in most patients. Interestingly, we observed a higher frequency of the CYP27A1 Arg395Cys allele in spinal CTX patients than expected. Unfortunately, absence of xanthomas may lead to a diagnosis and treatment delay and a worst outcome. As CDCA might prevent CTX features in asymptomatic patients, we suggest that CTX should be included in the new-born screening program. The dramatic disease progression seen after treatment interruption highlights the importance of not interrupting CDCA treatment. More generally, this case also illustrates the fragility of relying on orphan drugs for which the supply may not be guaranteed.

Abbreviations: C: Cervical

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2021.100719>.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Ethic statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements.

## Consent for publication

The patient provided its written consent to participate in this publication.

## Availability of data and supporting materials section

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

## Authors contribution

IA and CT conceived, planned and conceptualized the study. IA, DSM, BW, BCX and CT contributed to acquiring and interpreting clinical data. IA, CT and ASF wrote the initial manuscript. All authors critically reviewed, edited the manuscript and approved the final version as submitted. CT and ASF are responsible for the overall content and are the guarantor of the study.

## Declaration of Competing Interest

All authors state that they have no competing interests to declare. None of the authors accepted any reimbursements, fees or funds from any organization that may in any way gain or lose financially from the results of this study.

## Acknowledgements

We thank Dr. Veronica Castillo Cruz and Dr. Philippe Vuadens who were involved in the follow-up of the patient and available for sharing relevant information. We wish to express our gratitude to the patient who participated in this study and her family who were implicated in the follow-up of the patient. Through the generous sharing of her data, they will help in improving the diagnosis and hopefully the treatment of patients with diagnosis of spinal CTX.



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