Spinal Cerebrotendinous Xanthomatosis: An Easily Overlooked Treatable Disorder

Isis Atallah
Centre Hospitalier Universitaire Vaudois Departement universitaire de medecine et sante communautaires
Diego San Millán
Hopital du Valais
Wicki Benoît
Hopital du Valais
Belinda Campos-Xavier
Centre Hospitalier Universitaire Vaudois Departement des laboratoires
Andrea Superti-Furga
Universite de Lausanne Faculte de biologie et medecine
Christel Tran (Christel.Tran@chuv.ch)
Centre hospitalier universitaire vaudois Departement de medecine https://orcid.org/0000-0003-4158-536X

Research

Keywords: Cerebrotendinous xanthomatosis, spinal, medullar, clinical, chenodeoxycholic acid, genetic, CTX

Posted Date: July 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40976/v1

Abstract

Background:

Classic cerebrotendinous xanthomatosis (CTX; OMIM #213700) manifests itself in childhood with chronic diarrhea, juvenile cataracts, tendon xanthomas and neurological symptoms. Biallelic inactivation of *CYP27A1* is responsible for cholesterol 27-hydroxylation, leading 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.

Methods:

We report on a 28-year old woman diagnosed with CTX who worsened, under treatment, a spinal form of CTX. A review of spinal CTX in the literature is also described. Spinal CTX patients were identified by searching in Pubmed, EMBASE™ and Web of Science databases. Only patients with clinical features of spinal CTX and/or with a typical spinal MRI were included.

Results:

A woman 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. Treatment was discontinued several times and patient developed psychosis and an ataxospastic gait. Spinal MRI revealed new linear hyperintensities of the corticospinal and gracile tracts, compatible with spinal CTX.

Thirty-three patients with spinal CTX were identified in the literature. All patients presented pyramidal signs and 48% 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 (χ^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.

Background

Cerebrotendinous xanthomatosis (CTX), OMIM #213700, is a rare autosomal recessive disorder of bile acid biosynthesis due to pathogenic 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-α-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 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 glyconjugates in plasma and urine.

Brain MRI may reveal cerebral and cerebellar atrophy. More specific findings, such as bilateral hyperintensities of the dentate nuclei, cerebral and cerebellar white matter [6] are observed in more advanced stages. 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 paediatric 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. Medullary 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 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 xanthomathosis.

Case Presentation

A 38-year-old woman was evaluated for spastic paraparesis that had appeared in her twenties (Fig. 1). Her past medical history included chronic diarrhea, [illegible] y at age 25. She described muscle stiffness disturbing her for climbing stairs and running, calf

cramps and urinary frequency. She did not take any treatment and had normal schooling. Family history was not relevant neither for walking difficulties nor for cataracts. Neurological examination revealed spastic paraparesis with pyramidal signs more prominent on the left lower extremity without sensory impairment, 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). Medullary MRI was normal. 7 years later, due to progression of spastic paraparesis, CTX was considered. Cholestanol was increased to 64 µmol/L (3.3–12.5 µmol/L). A careful assessment found no tendinous xanthomas. Genetic analysis confirmed two monoallelic pathogenic variants in the gene *CYP27A1*: a missense variant (c.1183C > T; p.Arg395Cys) in exon 6 and a splicing variant (c.1184 + 1G > A; p.(?)) in a splice donor site in intron 6. Treatment with 750 mg/d chenodeoxycholic acid (CDCA) and 20 mg/d simvastatine were started together with periodic botulinum toxin leg injection to relieve spasticity. Three months later, diarrhea disappeared and no adverse effect was observed. One-year follow-up showed no progression of neurologic and radiologic signs.

As a result of CDCA withdrawal from the market one year after initiating treatment (end 2016), the patient was left untreated for a period of 16 months. Over this period, diarrhea recurred and walking worsened. She had increased stiffness with muscle pain and new apallesthesia of the lower limbs with onset of cerebellar ataxia. When CDCA treatment was reintroduced in april 2018, 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, subsequently, rapid worsening of her gait. She became rollator dependent. Neurologic evaluation showed a severe ataxospastic gait with knee recurvatum (additional files: video). ENMG was normal. Brain MRI was unchanged compared to an MRI performed 11 years before (2008) except for appearance of slight supratentorial brain atrophy, which could still be normal for age. The deep white matter abnormalities remained very subtle and the signal abnormality of the dentate nuclei 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 µmol/L; normal range 3.3–12.5 µmol/L), CDCA posology was increased to 250 mg t.i.d. Six months later, the patient had resolution of diarrhea and psychiatric symptoms but no improvement of gait.

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

Results

Database searches in Pubmed, Embase™ and Web of science identified 167 potential articles, 42 of them were duplicates. 35 articles underwent full text review and 12 articles and four abstracts met our inclusion criteria (Fig. 3): 30 patients were included. Hand search bibliography identified 3 cases reports (total 33 patients).

The main findings are summarized in Table 1. 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). All patients presented with a pyramidal syndrome associated in 16 patients (48%) with dorsal columns signs. Explicit mention of presence or absence of the three cardinal signs of CTX (cataracts, chronic diarrhea and xanthomas) were available for 27, 20 and 32 patients, respectively. Twenty-one patients were reported with cataracts (78%), 13 patients with diarrhea (65%) and 10 patients with xanthomas (31%). Only 2 patients (6%; n = 33) presented with the classic triad of CTX signs. Psychiatric symptoms were reported in 11 patients (33%), cerebellar signs in 10 patients (30%), seizures in 6 patients (18%), polyneuropathy in 6 patients (18%), intellectual deficiency in 4 patients (12%), dementia or cognitive decline in 6 patients (18%), dysarthria in 4 patients (12%), urinary troubles and dysphagia in 2 patients (6%). 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.

Table 1

Clinical, radiological and molecular data of 33 patients with spinal CTX reported in the literature and our case repor

ID	Sex	Country origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. \varvec$\mu$ mol/l (2–12)	Brain MRI	Medullar MRI	Treatmen Per day
1	M	Spain	31	34	+	-	+	+	+		89	Parieto-occipital and CWML	Anterior and posterior cervical and dorsal SCWML	CDCA 750 mg
2	F	Netherlands	20	23	-	+	+	+	+	Epilepsy	61	CWML	Lateral and dorsal SCWML	NA
3	F	Netherlands	24	45	-	+	+	+	+	Dysarthria, cerebellar signs	19	NA	NA	NA
4	M	Netherlands	30	33	+	-	+	+	+		NA	CWML	Lateral and dorsal SCWML	NA
5	M	Netherlands	35	43	-	-	+	+	+	Dysarthria, cerebellar signs, polyneuropathy	NA	CWML	Lateral and dorsal SCWML	NA
6	F	Netherlands	35	37	-	-	+	+	+		46	CWML	NA	NA
7	F	Netherlands	28	41	-	+	+	+	+		63	Normal	Lateral and dorsal SCWML	NA
8	F	Netherlands	28	36	-	+	+	+	+	Dementia	100	CWML	Lateral and dorsal SCWML	NA
9	M	Spain	11	27	-	NA	+	+	NA	Seizures	60	Hypersignal dentate nuclei	Normal	NA
10	M	Spain	12	27	-	NA	+	+	NA	Seizures, myoclonia	90	Cerebral atrophy, hypersignal dentate nuclei	Normal	NA
11	F	Switzerland	25	51	-	+	+	+	NA	Behavior troubles, cognitive decline, depression	139	CWML, periventricular WML and dentate nuclei	NA	CDCA
12	F	Switzerland	25	52	-	-	-	+	+		69	Normal	NA	CDCA
13	M	German	16	44	NA	NA	+	+	NA	Dementia, seizures	61 (4.9 mg/dl)	Cerebellar and dentate nuclei gliosis	NA	CDCA 1 g simvastat
14	M	Chili	34	39	+	+	+	+	+	Dementia, psychiatric disease, urinary incontinence	NA	Hyperintensities dentate nuclei and CWML	Posterior SCWML	CDCA 750 mg
15	NA	Spain	10	30	-	NA*	NA*	+	NA	Ataxia, seizures, neuropathy, psychiatric disease	66	Normal	NA	CDCA + Vi E + pravastat

ID	Sex	Country origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. \varvec$\mu$mol/l (2–12)	Brain MRI	Medullar MRI	Treatmen Per day
16	NA	Spain	12	23	-	NA*	+	+	NA	Ataxia, neuropathy, psychiatric disease	63	Normal	NA	CDCA + Vi E + pravastat
17	NA	Spain	18	32	-	NA*	NA*	+	NA	Seizures, ataxia, psychiatric disease	119	Atrophy demyelination	NA	CDCA + Vi E + atorvasta
18	NA	Spain	20	36	-	NA*	NA*	+	NA	Psychiatric disease	NA	Atrophy, leukoaraiosis	NA	CDCA + simvastat
19	NA	Spain	30	32	+	NA*	NA*	+	NA	Psychiatric disease	NA	Normal	NA	CDCA + vi E
20	NA	Spain	12	46	-	NA*	NA*	+	NA	ID, neuropathy, psychiatric disease	NA	Atrophy	NA	CDCA + vi E pravastat
21	NA	Spain	12	46	+	NA*	NA*	+	NA	ID, neuropathy, psychiatric disease	NA	Atrophy	NA	CDCA + statin + vi E
22	F		Child	30	+	NA	+	+	+	Truncal ataxia	NA	Increased signal in basal ganglia, dentate nucleus, pons, medulla oblongata	Increased posterior and lateral SCWML	NA

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ID	Sex	Country Origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. \varvec$\mu$ mol/l (2–12)	Brain MRI	Medullar MRI	Tre Pe
23	M	UK	24	27	-	+	-	+	NA	Urinary frequency, depression	112	Normal	Normal	NA
24	M	Japan	39	46	-	NA	-	+	+		30 (24.1 ug/ml)	CWML	Lateral corticospinal and gracile tracts hyperintensities	CD 75 dis + ato
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
26	M	Japan	65	77	+	+	-	+	NA		13 (10.4 ug/ml)	Normal	Cervical dorsal column hyperintensities	CD 75
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
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.	CD 50 inc 75
29	NA	NA	NA	NA	+	+	-	+	NA	Seizures	NA	Hypersignal dentate nuclei, diffuse cerebral and cerebellar atrophy		CD
30	F	Caucasso	16	56	+	+	+	+	NA	Ataxia, behavioral, dysarthria,cognitive impairment, learning difficulties	23 (1.81 mg/dl, n: <0.248)	Diffuse cerebral and CWML	SCWML	NA
31	F	Turkey	32	52	-	-	-	+	+		19 (15 ug/ml)	Bilateral symmetrical internal capsule, crus cerebri, and dentate nuclei lesions	Longitudinal SCWML	CD
32	F	Chili	22	22	-	+	+	+	NA		NA	CWML and dentate nuclei	Lateral and dorsal SCWML	CD

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
been previously described in patients with classic CTX. $^{\beta}$ 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 : Int
al cord white matter lesions ; WML : white matter lesions; ENMG : electroneuromyography; CDCA : che

ID	Sex	Country Origin	Onset age (y)	Age Dx (y)	X	D	C	PS	DCS	Other Neurological symptoms	Cholest. \varvec$\mu$ mol/l (2–12)	Brain MRI	Medullar MRI	Tre Pe
33	F	Caucasso	5	28	-	+	+	+	+	Neurocognitive regression, cerebellar signs, dementia	78 (6.24 mg/dL)	CWML, cerebral and cerebellar atrophy	Lateral and dorsal SCWML	CD 75
34	F	Switzerland	20	38	-	+	+	+	+	Cerebellar signs, psychiatric disease	64	Periventricular WML	Linear hyperintensitties	CD 50 inc 75

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 d been previously described in patients with classic CTX. [β] 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 : Int ; CWML : cerebellar white matter lesions ; SCWML : spinal cord white matter lesions ; WML : white matter lesions; ENMG : electroneuromyography; CDCA : che

Biochemical parameters were reported in 23 cases. All patients showed high plasma cholestanol levels (median levels of 63 µmol/L; IQR 30–89 µmol/L; N: 2–12 µmol/L). Cerebral MRI was performed in 31 patients and was normal in only 7 patients (25%). The most reported features observed in brain MRI of spinal CTX patients were cerebellar white matter lesions (n = 16; 48%), hypersignal of dentate nuclei (n = 9; 27%) and cerebral atrophy (n = 10; 30%). A spinal cord MRI was carried out in 19 patients. Linear hyperintensities of the lateral and posterior cortical tracts were observed in 16 patients (84%). Three patients had normal spinal MRI. In thirteen patients with typical spinal CTX features, spinal MRI was not performed.

Treatment information was available for 19 patients. All patients received CDCA treatment; this was associated with inhibitors of HMG-CoA reductase (pravastatine, simvastatine or atorvastatine) 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. Clinical outcome was reported in 13 patients, 4 patients showed disease improvement, 5 patients disease stabilisation and 4 patients disease progression despite CDCA treatment. Treatment delay was of 11.5 months (IQR 3.5–21.75 months), 16 months (IQR 2.5–32.5 months) and 18 months (IQR 12.25–30.5 months) for the groups of patients who showed disease improvement (n = 4), disease stabilization (n = 4) and disease progression (n = 4), respectively. 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 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* pathogenic variants observed in spinal CTX patients were Arg395Cys and Thr339Met, with an allele frequency of 17/ 46 (36%) and 8/46 (17%), respectively. Figure 3 shows different *CYP27A1* allele frequencies in the spinal CTX patients we reviewed compared with the cohort of 78 CTX patients described by Verrips in 2000 [12]. Since the spinal form of CTX was isolated only in 1999, this cohort may have included some spinal CTX patients. Nevertheless, we observed a statistically significant higher frequency of the *CYP27A1* allele p.Arg395Cys (p.Arg362Cys in old nomenclature) in patients with spinal CTX (allele frequency 17/46; 36%) than in the general cohort from Verrips et al. (13/156; 8%) (χ^2=23.02; p < 0.00001). In contrast, no difference was found for the p.Trp339Met allele (p.Thr306Met in old nomenclature) (χ^2=2.47; p = 0.12; allele frequency in the cohort from Verrips et al. 9.6%; 15/156). In addition, reanalysis of another previously reported cohort of 24 CTX patients (17 with classic and 7 with spinal CTX; 48 alleles) [13], 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%).

Discussion

Since the description of CTX in 1937 [14], more than 300 patients have been described worldwide. The classic form of CTX is the most frequent phenotype. A small proportion of patients develop the spinal form in which spastic paraparesis is the main clinical symptom and possibly the sole expression of the disease for many years. Because the presentation is not specific, spinal CTX patients are often initially misdiagnosed, especially when tendon xanthomas are not present or remain unnoticed. Among the 33 identified cases of spinal CTX, 69% did not have xanthomas, which possibly explains a diagnostic delay of 10 or more years (as in our case). The “CTX suspicion index” developed by Mignarri et al [15] emphasizes the importance of cataracts and diarrhea (rather than xanthomas): these signs were present in the majority of spinal cases we reviewed, including our case.

The first neurological signs in spinal CTX patients was spastic paraparesis with stiffness, hyperreflexia and positive Babinsky 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 delay nor intellectual deficiency, which are frequent in the juvenile form of CTX.

Early treatment with CDCA had positive impact on disease evolution and symptoms including bowel function, spasticity, psychiatric disease and/or cognitive function. Although in a minority of cases, CDCA was able to improve the spastic paraparesis, in the majority of cases CDCA seemed to have a limited impact

on the spinal cord syndrome. Our patient showed improvement of her chronic diarrhea and stabilization of neurological symptoms under CDCA treatment. However, after treatment was discontinued she rapidly developed psychiatric symptoms and worsening of gait (spastic paraparesis and gait disturbance). 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 [16]. This raised the hypothesis that abrupt interruption of CDCA could lead to a rebound of cholesterol biosynthesis with accumulation of toxic bile metabolites, which increases permeability of the blood brain barrier leading to brain and spinal accumulation of cholestanol [17, 18]. We raise the hypothesis of an existing compensatory mechanism (such as feedback inhibition) that might become deactivated during CDCA treatment, leading to an increased vulnerability of the central nervous system to toxic metabolites. Whatever the mechanism, continuity of treatment with CDCA appears to be an important target to avoid rebound effect and disease progression in CTX patients.

Imaging findings on brain MRI are non-specific and include periventricular white matter, basal ganglia, cerebral peduncles and dentate nuclei signal abnormalities and brain atrophy [6, 19]. In the present patient, brain MRI revealed questionable periventricular white matter “ground-glass” T2 hyperintensity and T2 hyperintensity of the dentate nuclei. These signal abnormalities were stable over a period of 11 years, during which a slight brain atrophy developed that could, however, correspond to normal ageing of the brain.

More characteristic for spinal CTX are signal abnormalities such as those observed in our patient involving the lateral cortico-spinal and gracilis tracts in the spinal cord [6, 20].

To date, there are 70 confirmed pathogenic variants causing CTX and 39 likely pathogenic variants in *CYP27A1* [21]. No clear genotype-phenotype correlation has been observed. However, the p.Arg395Cys allele seems to be significantly more frequent in spinal CTX patients than 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 [22]. Tridimensional protein modeling 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 [23].

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. Unfortunately, absence of xanthomas may be the cause of a significant delay in making the diagnosis and installing a disease-specific treatment with CDCA. We suggest that systematic use of the clinical “suspicion index “ proposed by Mignarri et al. might be helpful in recognizing CTX without xanthomas [15]. Spinal MRI studies seem to be useful as they may demonstrate signal abnormalities of the spinal cord suggestive of CTX and should be offered routinely. The *CYP27A1* p.Arg395Cys allele is significantly more frequent in spinal CTX patients than in classic CTX patients; the mechanistic basis of this association remains to be ascertained. The dramatic rebound effect seen after treatment interruption, possibly related to the complex feedback inhibition between CDCA and CYP7A1, 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

MRI: magnetic resonance imaging

CA: cholic acid

CDCA: Chenodeoxycholic acid

CTX: Cerebrotendinous xanthomatosis

ENMG: Electroneuromyography

IQR: Interquartile range

Declarations

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.

Competing interests

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.

Funding

This research received no external funding.

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.

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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Figures

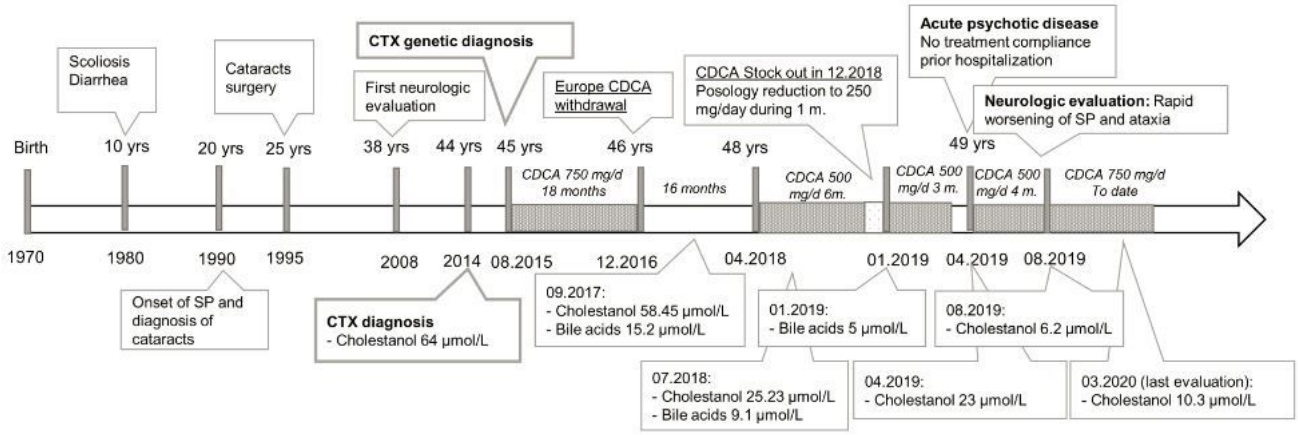

Figure 1

Patient timeline of clinical symptoms and biochemical values. Abbreviations: SP: spastic paraparesia; m: month; CDCA: chenodeoxycholic acid. Normal values for cholestanol (N: 0-15.45 µmol/L); bile acid (N: 0-10.02 µmol/L)

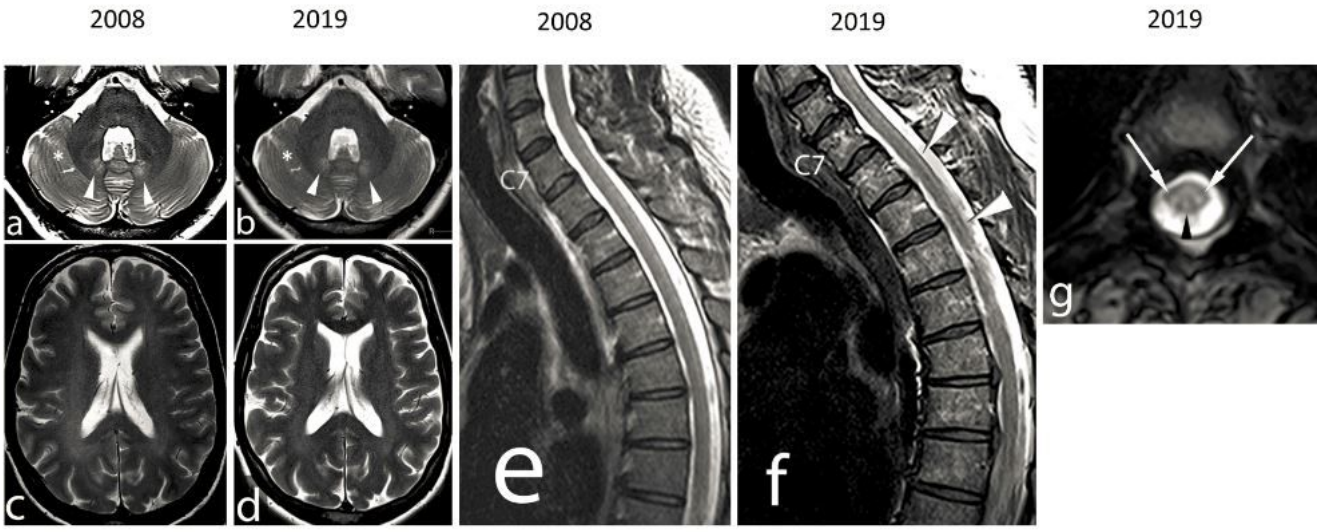

Figure 2

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

contrast material (gadolinium) uptake. Abbreviations: C: cervical

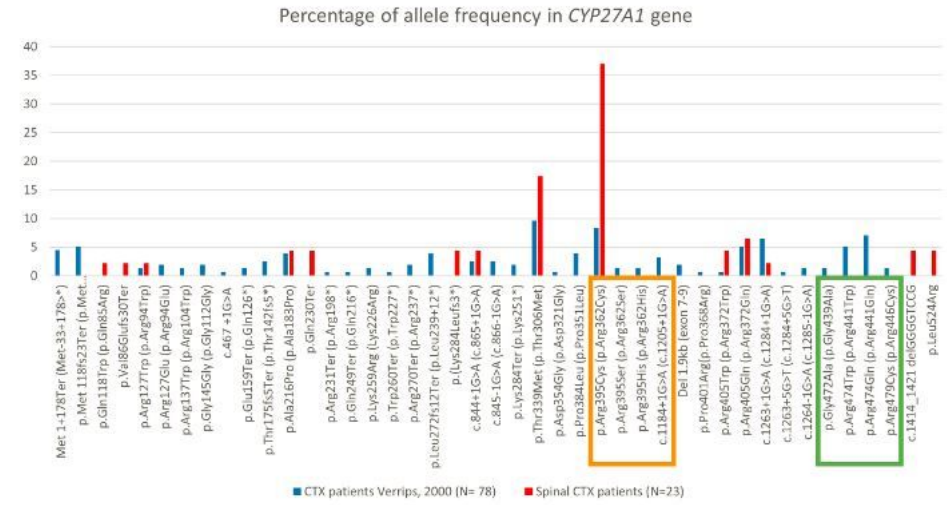

Figure 3

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.

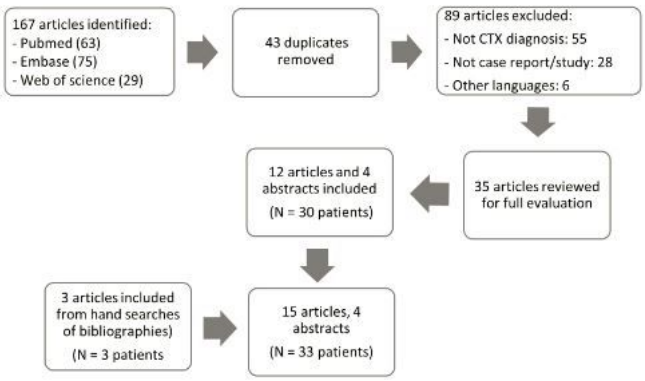

Figure 4

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) [12] and from all spinal CTX patients described in Table 1 (n=23, in red). Nucleotide or amino acid numbering (NM_000784.4 et NR_00075.1) are in new nomenclature [24] and in bracket in old nomenclature [22]. Premature stop codon = Ter (* 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).

Supplementary Files

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- CTXvideo06.07.20.m4v