J Inherit Metab Dis
DOI 10.1007/s10545-017-0093-8

REVIEW

Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX)

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Received: 10 July 2017 / Revised: 8 September 2017 / Accepted: 14 September 2017

Abstract Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disorder of bile acid synthesis caused by mutations in the cytochrome P450 *CYP27A1* gene that result in production of a defective sterol 27-hydroxylase enzyme. CTX is associated with abnormally high levels of cholestanol in the blood and accumulation of cholestanol and cholesterol in the brain, tendon xanthomas, and bile. Hallmark clinical manifestations of CTX include chronic diarrhea, bilateral cataracts, tendon xanthomas, and neurologic dysfunction. Although CTX is a rare disorder, it is thought to be underdiagnosed, as presenting signs and symptoms may be nonspecific with significant overlap with other more common conditions. There is marked variability in signs and symptoms, severity, and age of onset between patients. The disease course is progressive and potentially debilitating or fatal, particularly with respect to neurologic presentations that can include intellectual disability, autism, behavioral and psychiatric problems, and dementia, among others. Treatment with chenodeoxycholic acid (CDCA; chenodiol) is the current standard of care. CDCA can help restore normal sterol, bile acid, bile alcohol, and cholestanol levels. CDCA also appears to be generally effective in preventing adverse clinical manifestations of the disease from occurring or progressing if administered early enough. Improved screening and awareness of the condition may help facilitate early diagnosis and treatment.

Introduction

Cerebrotendinous xanthomatosis (CTX; OMIM #213700) is an autosomal recessive disorder of bile acid synthesis associated with abnormally high levels of cholestanol in the plasma and accumulation of cholestanol and cholesterol in tissues (Berginer et al. 2015; Moghadasian 2004; Salen 1971). Although considered a rare disorder, CTX may be underdiagnosed, as presenting signs and symptoms may be nonspecific and overlap with other more common conditions. There is marked variability in signs and symptoms, severity, and age of onset between patients (Verrips et al. 2000c). Hallmark clinical manifestations of CTX include chronic diarrhea, bilateral cataracts, tendon xanthomas, and neurologic dysfunction (Verrips et al. 2000c; Mignarri et al. 2014). The progressive disease course is potentially debilitating or fatal, particularly with respect to neurologic presentations that can include intellectual disability, autism, behavioral and psychiatric problems, and dementia, among others (Berginer et al. 2015; Stelten et al. 2017). We review key aspects of CTX, including its etiology, epidemiology, presentation, diagnosis, treatment, and prognosis, as well as future research directions. A literature search was performed using the PubMed database with the following search terms: [CYP27A1 OR (cholestanol accumulation) OR chenodeoxycholic OR CDCA] AND Xanthomatosis, Cerebrotendinous [MeSH Major Topic]. Additional references were identified by manual review of the reference lists of retrieved articles. References were selected based on relevance, and in the case of multiple

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Responsible Editor: Ronald JA Wanders

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Published online: 04 October 2017

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Etiology

CTX is caused by mutations in *CYP27A1* that result in production of a defective sterol 27-hydroxylase enzyme (CYP27A1; EC 1.14.15.15) (Cali et al. 1991). CYP27A1 is a mitochondrial enzyme that is ubiquitously expressed (Björkhem and Hansson 2010) and is responsible for catalyzing multiple hydroxylation reactions in cholesterol metabolism and bile acid synthesis, including the first step in the alternative bile acid synthesis pathway and 27-hydroxylation of bile acid intermediates in the classic synthesis pathway (Fig. 1) (Lorbek et al. 2012). In CTX, impairment in CYP27A1 activity, in combination with a limited ability to cleave the cholesterol side chain by the alternative microsomal C-25 hydroxylation pathway, results in diminished cholic acid formation and virtually no production of chenodeoxycholic acid (CDCA) (Salen 1971). Consequently, increased quantities of C-27 bile alcohols are produced and excreted as glucuronides mostly in the urine (Batta et al. 1987). In addition, upregulation of cholesterol synthesis and enhanced production of cholestanol (the 5α-dihydro derivative of cholesterol) (Salen and Grundy 1973) lead to increased plasma cholestanol and accumulation of cholestanol and cholesterol in tissues throughout the body, notably, the brain (primarily white matter), lens, and tendons (Berginer et al. 2015; Moghadasian 2004; Salen 1971); deposition in these tissues results in neurologic dysfunction, cataracts, and tendon xanthomas, respectively, all of which are characteristic of CTX (Verrips et al.

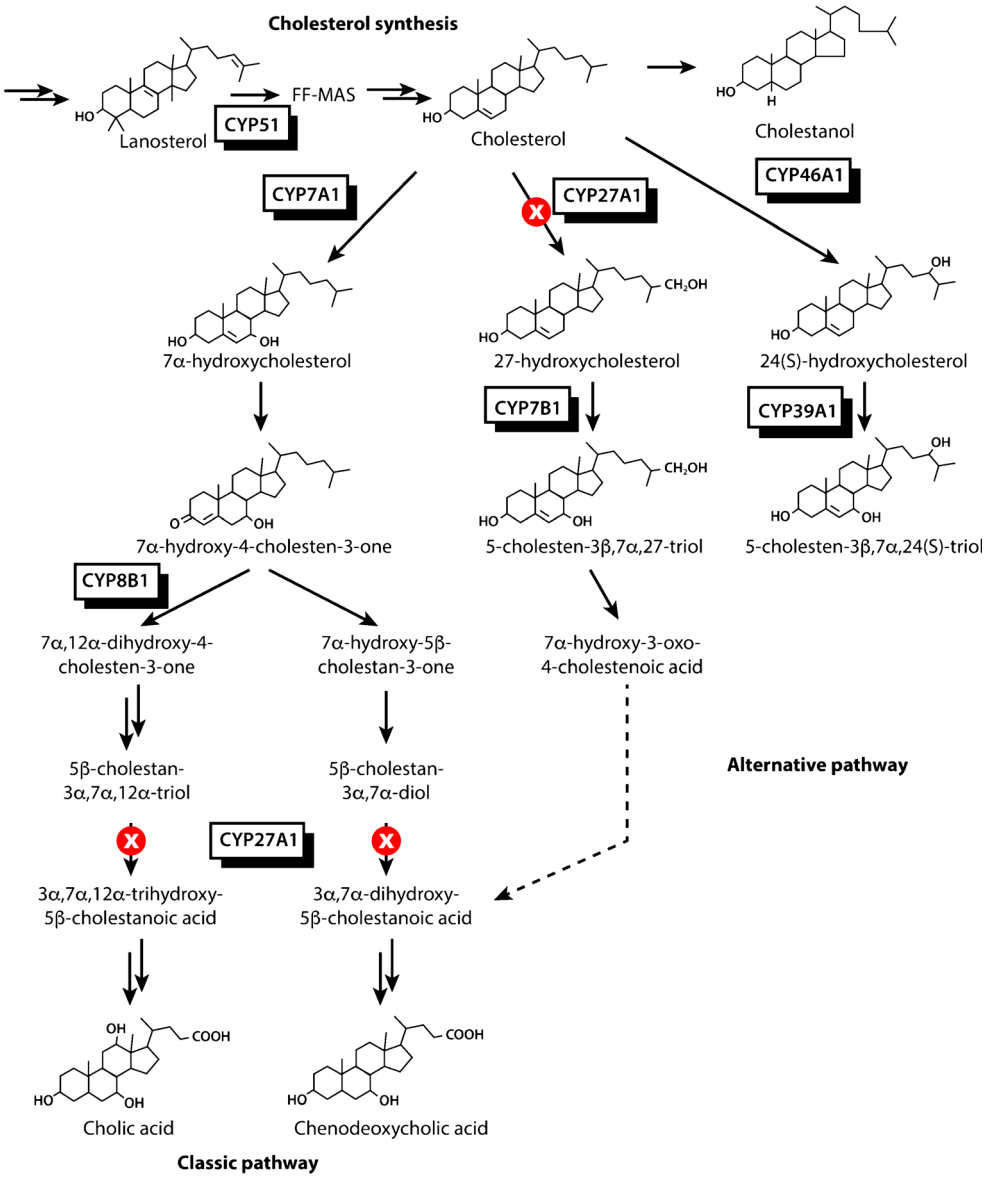

Fig. 1 Cholesterol and bile acid biosynthesis pathways. *Red* indicates changes in pathways in patients with cerebrotendinous xanthomatosis (CTX) (Salen et al. 1975). Adapted from Lorbek et al. (2012), with permission

2000c). In patients with CTX, cholestanol accounts for up to 10% of sterols in xanthomas, 10% in bile, and up to 50% in the brain (Salen et al. 1991; Salen 1971).

The mechanism by which cholestanol accumulates in the central nervous system (CNS) has not been fully established (Bavner et al. 2010). Currently available animal models for CTX (e.g., *cyp27a1* knockout mouse models) are suboptimal, as they do not demonstrate clear and consistent accumulation of cholestanol and/or bile alcohols or neurologic signs and symptoms associated with CTX (DeBarber et al. 2011; Rosen et al. 1998); poor genotype–phenotype correlation in CTX (Verrips et al. 2000a; Pilo-de-la-Fuente et al. 2011) also limits the ability to extrapolate from animal models. Studies that attempted to duplicate the CTX phenotype by feeding animals cholestanol-enriched diets found increased cholestanol levels in various tissues but not the brain (Berginer et al. 2015); such findings suggest that cholestanol does not efficiently pass the intact blood–brain barrier (BBB). Some data demonstrate an intact BBB in CTX patients, indicating that cholestanol accumulation may result from impaired removal of cholestanol or from synthesis of cholestanol in the brain from cholesterol or a circulating precursor that enters the brain (Bhattacharyya et al. 2007). The bile acid precursor, 7α-hydroxy-4-cholesten-3-one (which passes through the BBB at a markedly higher rate compared with cholestanol), can be efficiently converted to cholestanol by neurons, astrocytes, microglia, and human monocyte-derived macrophages, thereby leading to accumulation of cholestanol in the brain (Panzenboeck et al. 2007; Bavner et al. 2010). However, some data suggest that the BBB may be impaired in patients with CTX; specifically, the observation of increased cholestanol and apolipoprotein B concentrations in the cerebrospinal fluid (CSF) of CTX patients indicates enhanced permeability of the BBB (Salen et al. 1987). It has been suggested that this increased permeability may be a result of damage caused by circulating bile alcohol glucuronides in these patients (Batta et al. 1987; Berginer et al. 2015).

Over 99 different mutations implicated in CTX have been identified, including missense mutations, deletions, insertions, splice site mutations, and nonsense mutations (Verrips et al. 2000a; Appadurai et al. 2015; The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff 2017). No correlation has been established between specific mutations and specific clinical features or disease severity (i.e., no genotype-phenotype correlation) (Verrips et al. 2000a; Pilo-de-la-Fuente et al. 2011). In addition, phenotypic variation within families and among individuals with the same mutation has been reported, including a recently reported case of identical twins who presented with considerably different phenotypes (Verrips et al. 2000a; Pilo-de-la-Fuente et al. 2011; Zadori et al. 2017; Leitersdorf et al. 1993; Rosafio et al. 2016; Giraldo-Chica et al. 2015).

Epidemiology

CTX is considered a rare disease; it has been observed more frequently among female than male individuals (~55% vs 45%) (Verrips et al. 2000c). Several hundred cases have been reported, but the number of undiagnosed and possibly misdiagnosed cases is unknown (DeBarber et al. 2014b). Although epidemiologic data are limited and methodology differs among studies, available data suggest that CTX may be substantially underdiagnosed. For example, the prevalence of CTX in the USA among whites of European ancestry is estimated to be 3–5:100,000 individuals (Lorincz et al. 2005) and the incidence among Americans ~ 1:72,000 to 1:150,000 (Appadurai et al. 2015). Considering the population of >320 million (United States Census Bureau 2017), the number of cases from the USA alone should exceed the several hundred that have been reported worldwide to date. Estimates of the incidence of CTX vary by location. A genetic epidemiology study using the Exome Aggregation Consortium (ExAC) cohort of ~60,000 unrelated adults from global populations evaluated the allele frequency of 57 known and 29 predicted CTX-causing variants and found that estimated incidence of CTX was highest in South Asians and East Asians, followed by North Americans, Europeans, and Africans (Appadurai et al. 2015) (Table 1). Prevalence estimates vary considerably among different populations, with a particularly high prevalence reported for Jews of Moroccan origin and Druze in Israel (Table 1) (Berginer and Abeliovich 1981; Lorincz et al. 2005; Pilo-de-la-Fuente et al. 2011). Consistent with this, high CTX gene carrier frequencies have been reported for these populations (Berginer and Abeliovich 1981; Rosner et al. 2009; Falik-Zaccai et al. 2008) (Table 1). Genetic screening programs have been implemented in these communities at high risk for CTX (Falik-Zaccai et al. 2008; Rosner et al. 2009), enabling early identification and treatment of affected newborns, thereby preventing CTX symptoms in these individuals (Falik-Zaccai et al. 2008; Berginer et al. 2009).

Clinical presentation

CTX has a slow and progressive course, with diverse clinical presentations that may encompass varied combinations of neurologic and nonneurologic manifestations with onset as early as infancy or as late as adulthood (Fig. 2 (Mignarri et al. 2014; Fraidakis 2013; Berginer et al. 1993; Berginer and Abeliovich 1981; Verrips et al. 1999a; Waterreus et al. 1987; Verrips et al. 2000a; Berginer et al. 1994)). Clinical hallmarks include premature bilateral cataracts (88% of patients based on a review of selected international case series), intractable diarrhea (~50%), progressive neurologic signs and symptoms (pyramidal, 77%; cerebellar, 62%), and tendon xanthomas (69%) (Verrips et al. 2000c; Mignarri et al. 2014).

Table 1 Cerebrotendinous xanthomatosis (CTX) epidemiologic data

Region/Population	Estimate
Prevalence	
Israel/Jews of Moroccan origin[a]	6 per 70,000
USA/Whites of European ancestry[b]	3–5 per 100,000
Spain/total population[c]	1 per 1,800,000
Carrier frequencies	
Israel/Jews of Moroccan origin[a,d]	1:108; 1:70
Israel/Druze[e]	1:11
Incidence[f]	
South Asians	1:36,072–75,601
East Asians	1:64,267–64,712
North Americans	1:71,677–148,914
Europeans	1:134,970–461,358
Africans	1:263,222–468,624

[a] (Berginer and Abeliovich 1981); [b] (Lorincz et al. 2005); [c] (Pilo-de-la-Fuente et al. 2011); [d] (Rosner et al. 2009); [e] (Falik-Zaccai et al. 2008); [f] (Appadurai et al. 2015)

The earliest clinical signs associated with CTX are primarily nonneurologic. Neonatal cholestatic jaundice has been reported in several cases (Clayton et al. 2002; von Bahr et al. 2005). Chronic, unexplained, and often intractable diarrhea with onset in infancy or childhood is common and a key symptom associated with CTX and may persist into adulthood in some patients (Verrips et al. 2000c; Mignarri et al. 2014; Degos et al. 2016). Cataracts and tendon xanthomas reflect the accumulation of cholestanol and cholesterol in the affected tissues; although both are common, they do not occur in all patients (Berginer et al. 1984; Verrips et al. 1999a, 2000c; Moghadasian et al. 2002). Bilateral cataracts associated with CTX typically develop during childhood, sometimes preceding xanthomas and neurologic symptoms, but may also be seen in adults (Verrips et al. 2000c; Moghadasian 2004; Degos et al. 2016). Bilateral juvenile cataracts can be disabling, generally requiring treatment by adolescence; as such, cataracts are a common presenting feature (Verrips et al. 2000c; Berginer et al. 2015; Moghadasian 2004). Xanthomas also may begin to develop in childhood or adolescence and progressively enlarge over time (Moghadasian 2004; Berginer et al. 2015; Saute et al. 2015). Tendon xanthomas most often affect the Achilles tendon, although xanthomas may also develop on the fingers, tibial tuberosities, triceps, and plantar surfaces of the feet (Berginer et al. 1984; Moghadasian 2004; Berginer et al. 2015; Varman et al. 2016). Tuberous xanthomas located subcutaneously in the elbows, knees, and hands may also develop (Berginer et al. 2015), as well as xanthomas in the brain (Brienza et al. 2015; Bhattacharyya et al. 2007). Pes cavus deformity is another generally consistent feature of CTX (Berginer et al. 1993; Berginer and Abeliovich 1981).

Neurologic dysfunction is the most debilitating feature of CTX (Berginer et al. 2015). Neurologic symptoms are an important clinical hallmark of CTX, are present in many cases at diagnosis, and distinguish CTX from other lipid disorders (e.g., familial hypercholesterolemia; sitosterolemia) (Moghadasian 2004). A broad range of neurologic findings have been reported in patients with CTX, with low intelligence, pyramidal signs (e.g., spasticity, hyperreflexia, extensor plantar responses), cerebellar signs (e.g., ataxia, dysarthria,

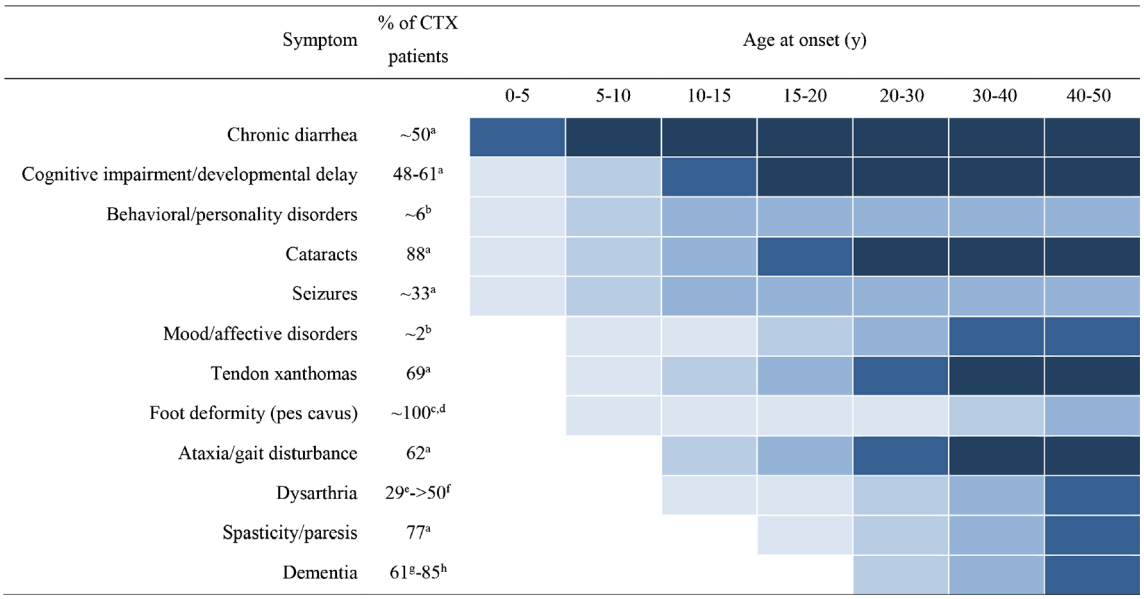

Fig. 2 Age at reported onset and cumulative frequency of symptoms in cerebrotendinous xanthomatosis (CTX) patients. *Darker color* indicates larger number of reports. [a](Mignarri et al. 2014); [b](Fraidakis 2013); [c](Berginer et al. 1993); [d](Berginer and Abeliovich 1981); [e](Verrips et al. 1999a); [f](Waterreus et al. 1987); [g](Verrips et al. 2000a); [h](Berginer et al. 1994)

nystagmus), and peripheral neuropathy among the most common (Verrips et al. 2000c; Pilo-de-la-Fuente et al. 2011; Ly et al. 2014); others include dementia, psychiatric symptoms, autism, epileptic seizures, and parkinsonism (e.g., spasticity, resting tremors) (Kuriyama et al. 1991b; Verrips et al. 2000c; Degos et al. 2016; Berginer et al. 2015; Stelten et al. 2017). Symptoms reflecting neurologic dysfunction, such as intellectual disability and gait disturbances, are common presenting symptoms (Pilo-de-la-Fuente et al. 2011).

Neurologic manifestations generally emerge during adolescence or early adulthood and worsen over time (Moghadasian 2004); however, developmental delays, intellectual disability, cognitive impairment, and learning difficulties may emerge during childhood (Lorincz et al. 2005; Larson et al. 2017; Degos et al. 2016; Fraidakis 2013). As the disease progresses, intellectual function continues to deteriorate and frank dementia may be present (Lorincz et al. 2005; Berginer et al. 2015). Psychiatric manifestations may appear during childhood or adolescence in the form of behavioral/personality disorders, sometimes presenting as autism, and may be associated with learning difficulties (Fraidakis 2013; Ly et al. 2014; Stelten et al. 2017). Attentional deficits, including attention deficit hyperactivity disorder (ADHD), may be presenting symptoms in young children (Fraidakis 2013; Ly et al. 2014). Alternatively, psychiatric disorders can emerge in advanced disease in older patients, often in the context of dementia, presenting as neuropsychiatric syndromes (Fraidakis 2013). Epileptic seizures may occur during childhood (Berginer et al. 2015); infantile spasms have also been reported, but only rarely (Larson et al. 2017).

Several additional clinical features associated with CTX have been described. Osteoporosis and an increased risk of fractures are often present in adults, although serum calcium, phosphate, and vitamin D metabolite levels are generally normal (Berginer et al. 1993; Federico et al. 1993; Martini et al. 2013). Premature atherosclerosis has been reported in several cases despite the fact that patients with CTX generally do not have significantly elevated plasma cholesterol levels (Salen 1971; Fujiyama et al. 1991; Valdivielso et al. 2004). Aside from cataracts, reported ocular manifestations include optic neuropathy, paleness of the optic disk, and premature retinal senescence (Cruysberg et al. 1995; Dotti et al. 2001). Pulmonary manifestations and xanthomas of the lung have also been reported (Salen 1971; Kawabata et al. 1998).

Diagnosis and testing

CTX is generally diagnosed based on clinical findings, biochemical testing, neuroimaging, and molecular genetic analysis. As previously noted, the clinical presentation can vary considerably in type, severity, and timing of symptoms. This variability may contribute to undiagnosed cases or delayed diagnosis. The onset of symptoms generally occurs during childhood or adolescence (mean age at onset from several large series: 9–19 years), diagnosis often does not occur until adulthood (mean age at diagnosis: 34–38 years), representing a considerable diagnostic delay (Mignarri et al. 2014). Some of the delay in diagnosis may be due to insufficient awareness of the condition. CTX patients, particularly those who present without tendon xanthomas, initially may be misdiagnosed with another condition, such as multiple sclerosis, peripheral neuropathy, mental retardation, and others. Although CTX can be easily differentiated from such conditions on the basis of elevated cholestanol levels, a lack of recognition of CTX can result in delayed diagnosis.

It has been suggested that the presence of two of four clinical hallmarks (premature cataracts, intractable diarrhea, progressive neurologic signs and symptoms, tendon xanthomas) should prompt thorough biochemical screening for CTX (Verrips et al. 2000c). Unexplained bilateral cataracts, particularly in children and adolescents, are a common manifestation that may be recognized by ophthalmologists (Cruysberg et al. 1995). The combination of juvenile cataracts and chronic diarrhea is particularly noteworthy (Cruysberg et al. 1991; Berginer et al. 2009), as these are among the earliest signs and symptoms. In addition, psychiatric disturbances, including ADHD, irritability, aggression, or oppositional–defiant disorder, in children and adolescents should prompt further evaluation, especially in the context of consanguinity (Fraidakis 2013). A suspicion index has been developed in which indicators such as family and common systemic and neurologic features are classified as very strong (100; e.g., sibling with CTX or tendon xanthoma), strong (50; e.g., juvenile cataract or ataxia), or moderate (25; e.g., early osteoporosis or epilepsy) (Mignarri et al. 2014). A total score ≥ 100 warranted serum cholestanol assessment, while elevated cholestanol or total score ≥ 200, with one very strong or four strong indicators, warranted *CYP27A1* gene analysis (Mignarri et al. 2014).

Disorders with features similar to CTX include conditions such as familial hypercholesterolemia and sitosterolemia (both of which may also present with xanthomas; sitosterolemia is also associated with elevated cholestanol and normal to elevated cholesterol levels), Smith-Lemli-Opitz syndrome (characterized by elevated 7-dehydrocholesterol, which may also be present in some patients with CTX), other inborn errors of bile acid metabolism, and nonspecific liver disease (Nie et al. 2014; Moghadasian et al. 2002; Björkhem et al. 2014; Salen et al. 1985). The presence of hallmark symptoms, such as cataracts, progressive neurologic symptoms, and chronic diarrhea, as well as the biochemical profile, can distinguish CTX from these disorders (Moghadasian et al. 2002; Berginer et al. 2015). Other conditions that present with clinical signs and symptoms that overlap with CTX may include multiple sclerosis, cerebellar ataxia, or mental retardation (as noted earlier, and patients with CTX initially may be incorrectly diagnosed with such conditions). The biochemical profile of CTX (i.e.,

elevated plasma cholestanol) distinguishes it from these conditions.

Several biochemical features characterize CTX and can aid in diagnosis. Cholestanol concentrations in plasma and tissues are increased, particularly in the brain, xanthomas, and bile (Salen 1971; Salen and Grundy 1973; Shore et al. 1981); plasma cholestanol measurement is often utilized as a diagnostic test. Increased quantities of bile alcohols (present as glucuronides) are found in bile, urine, and plasma and are biomarkers for CTX (Batta et al. 1987; Hoshita et al. 1980; Vaz and Ferdinandusse 2017); urine bile alcohol measurement is an excellent secondary diagnostic test. Bile acid profiles of plasma and urine may also be diagnostic of CTX depending on methodology, sample type and preparation, and experience of the laboratory performing the test (Vaz and Ferdinandusse 2017). Additional biochemical features have been described but may not be routinely tested in practice as part of the diagnostic process and/or may not be specific to CTX. CDCA is virtually absent in bile, and the CDCA to cholic acid ratio in bile is abnormally low (Salen 1971). Cholesterol concentrations in tissue are increased (Salen 1971), but plasma cholesterol levels [total, high-density lipoprotein (HDL), and/or low-density lipoprotein (LDL)] are low to normal, HDL composition is abnormal, and hepatic expression of LDL receptors is increased (Shore et al. 1981; Ballantyne et al. 1987). Concentrations of bile acid precursors in plasma (7α-hydroxy-4-cholesten-3-one and lathosterol) and bile (lathosterol) are increased, as are levels of plant sterols (campesterol and sitosterol) in plasma and bile (Mignarri et al. 2016; Kuriyama et al. 1991a; DeBarber et al. 2010). Elevated plant sterols and lathosterol are nonspecific findings. Recently, a multiplexed liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) quantifying a panel of plasma ketosterols (7α-hydroxy-4-cholesten-3-one, 7α,12α-dihydroxy-4-cholesten-3-one, and 7α,12α-dihydroxy-5β-cholestan-3-one) was developed and was shown to provide a more sensitive biochemical approach to discriminating between CTX-negative and -positive samples (DeBarber et al. 2014a). Cerebrospinal fluid levels of cholestanol, cholesterol, apolipoprotein B fragments, apolipoprotein-A1, and albumin are increased in CTX (Salen et al. 1987). Cholestanoic acids that have demonstrated neuroprotective effects in vitro and in vivo may be absent in the plasma of CTX patients (Theofilopoulos et al. 2014). Molecular genetic testing is useful for diagnosis confirmation; testing approaches can include single gene testing or multigene panels that include *CYP27A1*. Next-generation sequencing to screen for multiple genetic disorders simultaneously may facilitate earlier identification of CTX (Nicholls et al. 2015).

CNS features associated with CTX are often evident in imaging studies and electroencephalogram (EEG). Magnetic resonance imaging (MRI) studies show decreases in total brain volume (particularly gray matter) (Guerrera et al. 2010), cerebral and cerebellar atrophy (Pilo de la Fuente et al. 2008; Berginer et al. 1994), extensive white mater lesions of the spinal cord (in patients with spinal xanthomatosis) (Verrips et al. 1999a; Yanagihashi et al. 2016), and bilateral hyperintensity of the dentate nuclei and surrounding white matter (considered characteristic of CTX; Fig. 3) (De Stefano et al. 2001; Guerrera et al. 2010; Yoshinaga et al. 2014). Increased peaks of choline on MR spectroscopy (MRS) have also been observed and may be useful to monitor response to therapy (Degos et al. 2016); abnormal lipid peaks have also been detected on MRS, although their clinical significance is uncertain (Embirucu et al. 2010). Reported computed tomography (CT) abnormalities include cerebellar white matter hypodensities above and below the tentorium (Berginer et al. 1984; Waterreus et al. 1987). EEG abnormalities are common and may be characterized by diffuse irregular slow theta and delta activity with frequent sharp wave discharges; however, these abnormalities are not unique to CTX (Waterreus et al. 1987; Berginer et al. 1984; Berginer et al. 1982; Tokimura et al. 1992).

Peripheral nervous system (PNS) irregularities associated with neuropathy are evident on various neurophysiologic examinations. Abnormalities in patients with CTX have been reported for visual evoked potential (VEP), somatosensory evoked potential (SSEP), brainstem auditory evoked potential (BAEP), and nerve conduction velocity (NCV) studies, which may reflect delayed central conduction (Pilo-de-la-Fuente et al. 2011; Tokimura et al. 1992; Ginanneschi et al. 2013). Electromyography (EMG)/NCV findings demonstrating motor or sensorimotor axonal neuropathy, demyelinating neuropathy, and mixed neuropathy have been reported (Pilo-de-la-Fuente et al. 2011; Ginanneschi et al. 2013; Verrips et al. 2000b). Electron-dense deposits and crystal formation are a consistent histologic feature in liver biopsies from CTX patients. These microscopic deposits, diffusely located in cytoplasm, may result from overproduction and accumulation of bile acid precursors (Berginer et al. 2015).

Treatment

CDCA represents the standard of care for treating patients with CTX. Following the discovery that the biliary bile acid composition of patients with CTX is abnormal, with a virtual absence of CDCA (Salen 1971), administration of CDCA orally was evaluated and shown to correct the biochemical abnormalities and improve clinical symptoms in 17 patients with CTX (Berginer et al. 1984). Alternative treatments have been examined, including hydrophilic bile acids (Batta et al. 2004; Koopman et al. 1985), cholestyramine (Batta et al. 2004), clofibrate (Salen and Grundy 1973), statins (alone or in combination with CDCA) (Peynet et al. 1991; Salen et al. 1994; Verrips et al. 1999b), and LDL apheresis (Mimura et al.

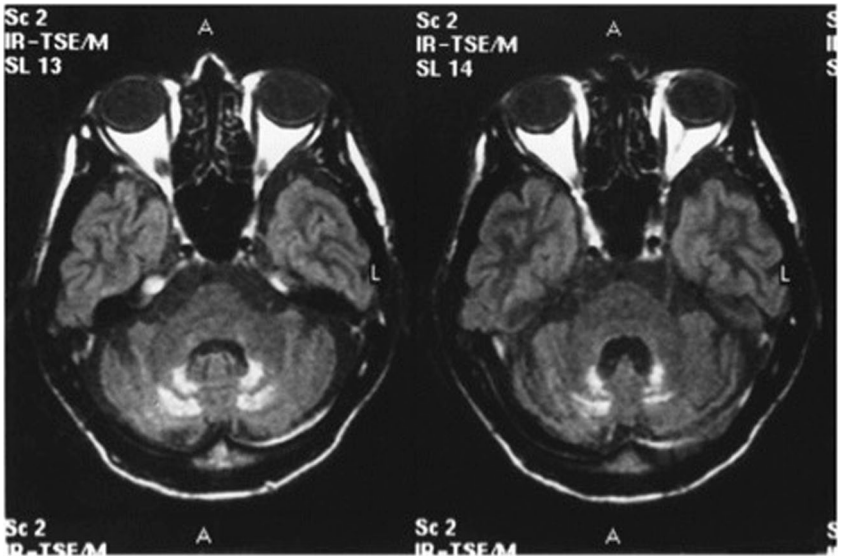

Fig. 3 Fluid-attenuated inversion recovery (FLAIR) images in transverse orientation showing a bilateral hyperintensity of the dentate nuclei and the surrounding cerebellar white matter. Reprinted from De Stefano et al. (2001) , with permission

1993; Dotti et al. 2004), but have generally shown limited efficacy in inhibiting abnormal bile acid synthesis, reducing and maintaining reduced cholestanol levels, and/or demonstrating significant clinical improvement. Cholic acid has shown some efficacy (Koopman et al. 1985), but it has not been widely tested and may not inhibit cholestanol formation to the same extent as CDCA (Huidekoper et al. 2016). Surgical removal of tendon xanthomas is not recommended, except when acute cord compression or pressure relief is needed for emergent therapy), as xanthomas can regrow rapidly in patients with uncontrolled CTX (Berginer et al. 2015).

CDCA reduces abnormal bile acid synthesis via direct inhibition of the cholesterol 7α-hydroxylase enzyme (CYP7A1; EC 1.14.14.23) and via negative feedback on cholesterol biosynthesis (Berginer et al. 1984; Salen et al. 1975). Specifically, it inhibits CYP7A1 through a pathway mediated by nuclear receptor farnesoid X receptor (FXR) (Ellis et al. 2003). Suppression of CYP7A1 reduces production of cholestanol and normalizes levels of 7α-hydroxy-4-cholesten-3-one (Björkhem et al. 1987), a bile acid precursor capable of efficient transfer across the BBB and which is converted to cholestanol in neuronal glial cells (Panzenboeck et al. 2007). CDCA also reduces susceptibility of LDL to oxidative modification and enhances cholesteryl ester transfer protein (CETP) activity, affecting two processes thought to contribute to the formation of xanthomas (Kinoshita et al. 2004). It also inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG CoA reductase) (Salen et al. 1975), thereby suppressing cholesterol production and xanthoma formation. Several aspects of CDCA and its mechanism of action differentiate it from cholic acid. CTX patients have a normal or higher concentration of cholic acid than controls and a pool size enriched for cholic acid (Beppu et al. 1982). CDCA is the most potent, naturally occurring FXR ligand, while there are conflicting results as to whether cholic acid is able to reduce CYP7A1 expression (Ellis et al. 2003). In addition, cholic acid has no effect on feedback inhibition of HMG CoA reductase, as the enzyme is not a pharmacological target for cholic acid (Einarsson et al. 2001).

CDCA is effective in improving both biochemical abnormalities and clinical features of CTX. However, advanced symptoms that have been present for many years are unlikely to significantly improve (Berginer et al. 2009). It reduces levels of circulating cholestanol, other sterols (e.g., lanosterol, campesterol, sitosterol), and bile acid precursors (e.g., 7-α-hydroxy-4-cholesten-3-one) (Berginer et al. 1984; Kuriyama et al. 1994; Salen et al. 1975; Björkhem et al. 1987; Mignarri et al. 2016; DeBarber et al. 2010); bile alcohol levels in plasma, bile, and urine (Batta et al. 1987; Batta et al. 2004); and cholic acid levels (Salen et al. 1994). It increases CDCA levels in bile (Salen et al. 1994), and normalizes lipid levels (Kuriyama et al. 1994; Tint et al. 1989). CDCA treatment typically does not significantly reduce tendon xanthomas or improve cataracts (Berginer et al. 1984; Mondelli et al. 2001), but can stabilize or improve neurologic manifestations, including cognitive deterioration, pyramidal tract signs, and cerebellar deficits (Berginer et al. 1984; Mondelli et al. 2001; van Heijst et al. 1998). It does, however, reduce abnormally elevated levels of cholestanol, apolipoprotein-B, apolipoprotein-A1, and albumin in the CSF and re-establishes the selective impermeability of the BBB (Salen et al. 1987). Improvements in neurophysiologic investigations: NCV and/or VEP (Ginanneschi et al. 2013; Mondelli et al. 1992; Mondelli et al. 2001), EEG (Berginer et al. 1984; van Heijst et al. 1998), and bone mineral density (BMD) (Federico et al. 1993; Martini et al. 2013) have also been reported.

The beneficial effects of CDCA treatment on neurologic manifestations are generally greater when treatment is started earlier in the disease course (Yahalom et al. 2013), suggesting that damage due to deposition of cholesterol and cholestanol in nerve tissues may be reversible and related clinical

symptoms preventable, up to a point (Berginer et al. 2015; Brienza et al. 2015). Further, initiating treatment in patients who are diagnosed before the onset of clinical symptoms may be effective in preventing irreversible multiorgan damage and the onset of clinical symptoms (Berginer et al. 2009).

Few specific adverse events or safety concerns have been reported for CTX patients treated with CDCA, with several reports indicating no adverse events (Berginer et al. 1984; Berginer et al. 2009). Hepatotoxicity has been specifically but rarely reported. One patient in a small study of combined CDCA and pravastatin treatment had to discontinue CDCA due to liver dysfunction after 6 months (Kuriyama et al. 1994). Another study reported that one patient switched from CDCA to cholic acid treatment due to side effects of severe diarrhea, nausea, and abnormal liver tests (Waterreus et al. 1987). Hepatotoxicity was also reported in an infant after 6 weeks of treatment at 15 mg/kg per day; treatment was discontinued until liver size and function normalized and restarted at a dose of 5 mg/kg per day, with no further evidence of hepatotoxicity and with adequate metabolic control (Huidekoper et al. 2016). The safety of CDCA in pregnant patients has not been extensively studied or reported. Published data include reports of five patients with CTX who became pregnant and gave birth to healthy babies while on CDCA (Moghadasian et al. 2002; Yahalom et al. 2013); while abstaining from CDCA treatment, some of these patients experienced difficulties conceiving, miscarriages, and stillbirths at term (Yahalom et al. 2013). These difficulties with pregnancy in patients with untreated CTX are consistent with reports of fetal and/or infant deaths in families with CTX and premature births and mental retardation in children born to mothers with CTX (Clayton et al. 2002; Berginer et al. 1988), suggesting that pregnancy in untreated CTX may be a high-risk condition. The positive outcomes for patients who received CDCA during pregnancy are consistent with the personal experience of the author (GS), who had five patients treated with CDCA, all of whom had uneventful pregnancies and gave birth to normal children.

CDCA is available in the USA (Chenodal®, Retrophin, Inc), but is currently only approved for patients with radiolucent stones in well-opacifying gallbladders in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age (Manchester Pharmaceuticals, Inc, 2009). Use in gallstone disease, however, is nil, or nearly so. CDCA also was recently approved in the European Union (EU) as an orphan drug indicated for treating CTX in infants (≥1 month), children, adolescents, and adults (European Medicines Agency 2017). The usual dose for adults is 750 mg per day; 15 mg/kg per day may be used for children (van Heijst et al. 1998), although a lower dosage of 5 mg/kg per day may be preferable for younger children and infants (Huidekoper et al. 2016). CDCA should be administered in three divided daily doses. It is is a long-term treatment, as continued administration is necessary to maintain its therapeutic effects.

Generally, neurologic and neuropsychologic evaluation, plasma cholestanol concentration, brain MRI, echocardiography, and total-body bone density should be evaluated annually; more frequent surveillance may be indicated in newly diagnosed patients until biochemical indicators of disease stabilize. Of note, cholestanol levels may require considerable time to return to a normal range; in one study, plasma cholestanol consistently decreased over time with CDCA treatment but took nearly 2 years to reach normal levels (reflecting that accumulated cholestanol was continuously being mobilized and excreted during treatment) (Salen et al. 1994). Assessment of plasma cholestanol also may be useful in monitoring patient adherence to treatment. In addition, 7α-hydroxy-4-cholesten-3-one quantification may be a more sensitive indicator of response to treatment such that it may be reasonable to follow those levels annually (DeBarber et al. 2010). Urine bile alcohols, which diminish markedly upon initiation of CDCA treatment, are not routinely measured at regular intervals after diagnosis; similarly, lipid profiles and fat-soluble vitamin concentrations are not routinely followed, unless there are significant abnormalities.

Future research

Increasing awareness is a key step in improving outcomes for patients with CTX, who are often diagnosed in adulthood after a significant delay (~20 years) between symptom onset and diagnosis (Degos et al. 2016; Pilo-de-la-Fuente et al. 2011), which likely reflects difficulty in recognizing the signs of disease. Evidence of improved outcomes with earlier initiation of treatment (Yahalom et al. 2013) underscores the need for better recognition and earlier diagnosis of patients with CTX to reduce morbidity and mortality rates.

Expanded screening efforts may help with earlier patient identification. Including CTX in universal newborn screening programs could allow early detection and intervention, and in light of the potential benefits of early recognition and treatment, should be added to newborn screening programs when a validated method is available. Rapid isotope-dilution LC-ESI/MS/MS quantification of the ketosterol bile acid precursor, 7α,12α-dihydroxy-4-cholesten-3-one, in dried bloodspot samples of newborns effectively discriminates between CTX and unaffected newborns, suggesting that 7α,12α-dihydroxy-4-cholesten-3-one may be a useful test marker for screening (Bleyle et al. 2016). A recent study evaluating a new dried blood spot screening assay for CTX based on different ratios between the accumulating cholestanetetrol glucuronide (tetrol) and specific bile acids/bile acid intermediates taurochenodeoxycholic acid (t-CDCA) and taurotrihydroxycholestanoic acid (t-THCA), showed that the tetrol:t–CDCA ratio had excellent separation between CTX patients and controls, Zellweger patients, and newborns with cholestasis, suggesting that this derived

biomarker has the potential for use in newborn screening programs (Vaz et al. 2017). Implementation of routine testing in patients who present with clinical hallmarks of CTX—perhaps most notably, children who present with juvenile cataracts and chronic diarrhea (Cruysberg et al. 1991; Berginer et al. 2009), is another potential strategy. Ophthalmologists, in particular, have an opportunity to recognize patients with CTX, since bilateral juvenile cataracts are one of its early symptoms.

Several unmet needs in CTX would benefit from future research, such as better epidemiologic studies to more accurately describe its incidence and prevalence and further investigation of disease mechanisms to help definitively determine the pathway by which cholestanol is produced. In the absence of a genotype–phenotype correlation, studies are needed to identify important factors in determining disease course. Research on long-term outcomes may improve our understanding as to why some patients have symptom progression despite (apparently) optimal treatment with CDCA. Finally, development of new treatment approaches, such as gene therapy, may one day provide a much-needed cure for CTX.

Acknowledgements The authors thank Sherri D. Jones, PharmD, of MedVal Scientific Information Services, LLC for medical writing and editorial assistance, which was funded by Retrophin, Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research:" The GPP3 Guidelines.

Compliance with ethical standards

Conflict of interest Gerald Salen has no conflict of interest to report.

Robert D. Steiner has received consulting fees from Retrophin but was not compensated for work related to this manuscript.

Role of sponsor Retrophin, Inc. provided financial support to MedVal Scientific Information Services, LLC for assistance with medical writing and was given the opportunity to review the manuscript for medical accuracy but played no role in data acquisition, literature analysis/interpretation, or manuscript writing. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

Informed consent/animal rights This article is a review of previously published work and does not present any new previously unpublished studies with human or animal subjects performed by the any of the authors.

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