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Review

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Cerebrotendinous Xanthomatosis: Molecular Pathogenesis, Clinical Spectrum, Diagnosis, and Disease-Modifying Treatments

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Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disorder caused by mutations in the *CYP27A1* gene, which encodes the mitochondrial enzyme sterol 27-hydroxylase. Decreased sterol 27-hydroxylase activity results in impaired bile acid synthesis, leading to reduced production of bile acids, especially chenodeoxycholic acid (CDCA), as well as elevated serum cholestanol and urine bile alcohols. The accumulation of cholestanol and cholesterol mainly in the brain, lenses, and tendons results in the characteristic clinical manifestations of CTX. Clinical presentation is characterized by systemic symptoms including neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and a broad range of neuropsychiatric manifestations. The combinations of symptoms vary from patient to patient and the presenting symptoms, especially in the early disease phase, may be nonspecific, which leads to a substantial diagnostic delay or underdiagnosis. Replacement of CDCA has been approved as a first-line treatment for CTX, and can lead to biochemical and clinical improvements. However, the effect of CDCA treatment is limited once significant neuropsychiatric manifestations are established. The age at diagnosis and initiation of CDCA treatment correlate with the prognosis of patients with CTX. Therefore, early diagnosis and subsequent treatment initiation are essential.

Key words: **Cerebrotendinous xanthomatosis, CTX, CYP27A1, Cholestanol, Chenodeoxycholic acid**

Introduction

Cerebrotendinous xanthomatosis (CTX: OMIM#213700), first described by van Bogaert *et al.* in 1937, is a rare autosomal-recessive lipid storage disease caused by deficiency of the mitochondrial cytochrome P 450 enzyme, sterol 27-hydroxylase (CYP27A1, EC 1.14.15.15) due to mutations in the *CYP27A1* gene[1]. Clinical presentation is characterized by neonatal jaundice or cholestasis, refractory diarrhea, juvenile cataracts, tendon xanthomas, osteoporosis, coronary heart disease, and progressive neuropsychiatric disturbances including mental retardation or dementia, psychiatric symptoms, pyramidal and cerebellar signs, progressive myelopathy, peripheral neuropathy, extrapyramidal manifestations, and seizures[2-9]. CTX is associated with considerable variability in clinical manifestations among patients and even within the same family[2]. The broad and diverse clinical symptoms cause a substantial diagnostic delay[2-4, 9]. Replacement treatment with chenodeoxycholic acid (CDCA) in the early stage of the disease has been reported to improve or even prevent clinical symptoms of CTX[10, 11]; however, after significant neurological pathology is established, the effect of the treatment is limited and deterioration of clinical manifestations may continue[3, 8, 12, 13]. Therefore, it is crucial to treat CTX patients at the initial stage of the disease. In this article, we provide the current understanding of the underlying pathomechanisms, clinical manifestations, diagnosis, and treatment of CTX.

Pathophysiology

CTX is caused by mutations in the *CYP27A1* gene encoding sterol 27-hydroxylase, a key enzyme in the bile acid synthesis pathway. A schematic

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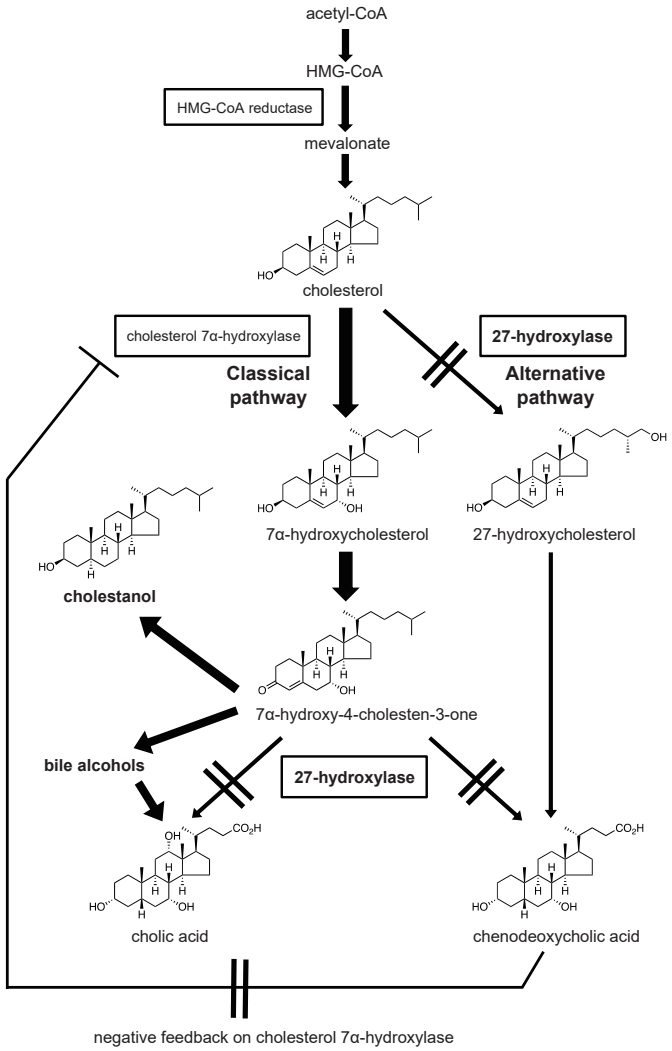

Fig. 1. Impaired bile acid synthesis in cerebrotendinous xanthomatosis (CTX)

In CTX, mutations in the *CYP27A1* gene lead to sterol 27-hydroxylase deficiency, resulting in reduced production of chenodeoxycholic acid and upregulation of the rate-limiting enzyme in the bile acid synthesis pathway, cholesterol 7α-hydroxylase. Increased levels of serum cholestanol and urinary bile alcohols are biological markers in CTX. HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA.

representation of the bile acid synthesis pathway is shown in **Fig. 1**. The classical pathway is initiated by 7α-hydroxylation of cholesterol, catalyzed by the rate-limiting enzyme cholesterol 7α-hydroxylase. The alternative pathway is initiated by 27-hydroxylation of cholesterol, which is catalyzed by sterol 27-hydroxylase. Decreased activity of sterol 27-hydroxylase leads to impaired bile acid synthesis in both the classical and alternative pathways[14], resulting in reduced production of bile acids, especially CDCA, and to a lesser extent cholic acid[15]. The absence of a negative feedback effect of CDCA on cholesterol 7α-hydroxylase accelerates these metabolic abnormalities, leading to increased levels of the bile acid intermediate 7α-hydroxy-4-cholesten-3-one as a precursor for cholestanol and bile alcohols[16]. Elevated serum cholestanol and urine bile alcohols are the biochemical diagnostic hallmarks in CTX. Consequently, increased cholesterol metabolites, such as cholestanol, accumulate mainly in the brain, lenses, and tendons, leading to the characteristic clinical manifestations of CTX. Elevated levels of cholestanol have been found in the serum and tissues, including those of the central nervous system, tendon xanthomas, and atheromatous lesions, in CTX patients. Although the cholestanol-to-cholesterol ratios of various tissues were higher than that of serum, cholesterol was more abundant than cholestanol in both serum and tissues[17]. Cholestanol is widely used as a diagnostic marker but the usefulness of 7α-hydroxy-4-cholesten-3-one

quantification in both the diagnosis and monitoring of CTX has also been reported[18]. It has also been shown that quantification of a panel of plasma ketosterol bile acid precursors (7α-hydroxy-4-cholesten-3-one, 7α,12α-dihydroxy-4-cholesten-3-one, and 7α,12α-dihydroxy-5β-cholestan-3-one) provides a more sensitive biochemical approach when compared with measurement of cholestanol[19].

In 1968, Menkes *et al.* discovered accumulation of cholestanol and cholesterol in the cerebrum and cerebellum of patients with CTX[20]. Although the mechanism by which cholestanol accumulates in the brain remains unclear, one possible explanation is that the bile acid precursor 7α-hydroxy-4-cholesten-3-one, which passes through the blood-brain barrier (BBB) more efficiently than cholestanol, can be converted to cholestanol by neurons, astrocytes, microglia, and human monocyte-derived macrophages[21, 22]. Another possible explanation is impairment of the BBB. Increased levels of cholestanol and apolipoprotein B were observed in the cerebrospinal fluid of patients with CTX, indicating disrupted function of the BBB[23]. It has also been proposed that large plasma bile alcohol glucuronides play a role in the abnormal BBB permeability in CTX, leading to increased transport of cholestanol and cholesterol in the brain[24].

Although the major pathway for production of cholestanol in CTX has been clarified, little is known about its metabolism. Under normal conditions, the 7α-hydroxy-4-cholesten-3-one-dependent pathway accounts for only about 30% of cholestanol biosynthesis in the brain, and cerebral cholestanol is mainly formed from cholesterol[25]. Using *Cyp27a1* and *Cyp46a1* knockout mice, Mast *et al.* demonstrated that CYP46A1 plays an important role in cholestanol removal from the brain and that CYP27A1 deficiency results in a preferential increase in cholestanol in the cerebellum[25].

CTX patients develop premature atherosclerosis and xanthomas despite normal serum cholesterol concentrations. However, abundant deposits of cholesterol are detected in addition to cholestanol in the respective lesions in CTX[17]. Although the mechanism leading to premature arteriosclerosis and tendon xanthomas in CTX remains unclear, reduced capacity for reverse cholesterol transport has been proposed as a possible cause[26-31]. Sterol 27-hydroxylase, which is expressed in macrophages, endothelial cells, and tenocytes as well as in the liver, seems to contribute to the transport of peripheral cholesterol to the liver by transforming intracellular cholesterol into 27-hydroxycholesterol, which has a higher capacity for passing through lipophilic membranes compared with cholesterol[26-28]. In addition, 27-hydroxycholesterol is an endogenous ligand for liver X receptor (LXR). LXR activation induces upregulation of ATP-binding cassette transporter A1 (ABCA1) expression, leading to increased cholesterol efflux[29-31]. Fu *et al.* demonstrated that upregulation of ABCA1 in response to cholesterol loading was impaired in primary fibroblasts derived from a CTX patient[29]. In addition, since 27-hydroxycholesterol was found to be the major oxysterol in human atherosclerotic lesions[28], extrahepatic sterol 27-hydroxylase is thought to be an anti-atherosclerotic enzyme. Absence of the two above defense mechanisms may contribute to premature atherosclerosis and xanthoma formation in CTX.

Epidemiology

CTX patients have been reported worldwide but prevalence of the disease is considered to be underestimated[32]. Based on the carrier frequency of the pathogenic *CYP27A1* c.1183C>T (p.R395C) mutation in 115 control subjects, the prevalence of CTX in the USA among Caucasians of European ancestry was estimated to be 3-5:100,000 individuals[32]. Pilo-de-la-Fuente *et al.* estimated a minimum prevalence of 1/1,8000,000 individuals in Spain[3]. Estimates of the incidence of CTX vary among locations. A recent genetic epidemiological study based on the Exome Aggregation Consortium (ExAC) cohort, a large cohort of over 60,000 unrelated subjects, evaluated the allele frequency of 57 known and 29 predicted CTX-causing variants and estimated the incidence of CTX to be 1:134,970-1:461,358 in Europeans, 1:263,222-1:468,624 in Africans, 1:71,677-1:148,914 in Americans, 1:64,247-1:64,712 in East Asians, and 1:36,072-1:75,601 in South Asians[33]. Prevalence among Jews of Moroccan origin and the Druze sect in Israel has been reported to be particularly high[34, 35].

Molecular Genetics

In 1991, human sterol 27-hydroxylase cDNA was isolated from a liver cDNA library. The *CYP27A1* gene consists of nine exons and eight introns and spans 18.6 kb of DNA on chromosome 2q33-qter[36, 37]. Sterol 27-hydroxylase consists of a 33-residue mitochondrial signal sequence followed by a mature protein of 498 amino acids containing putative binding sites for heme and adrenodoxin[1]. Cali *et al.* first identified two *CYP27A1* missense mutations, p.R395C and p.R479C, in patients with CTX and demonstrated that a loss-of-function mechanism is responsible for CTX[1].

CYP27A1 is the only gene known to be

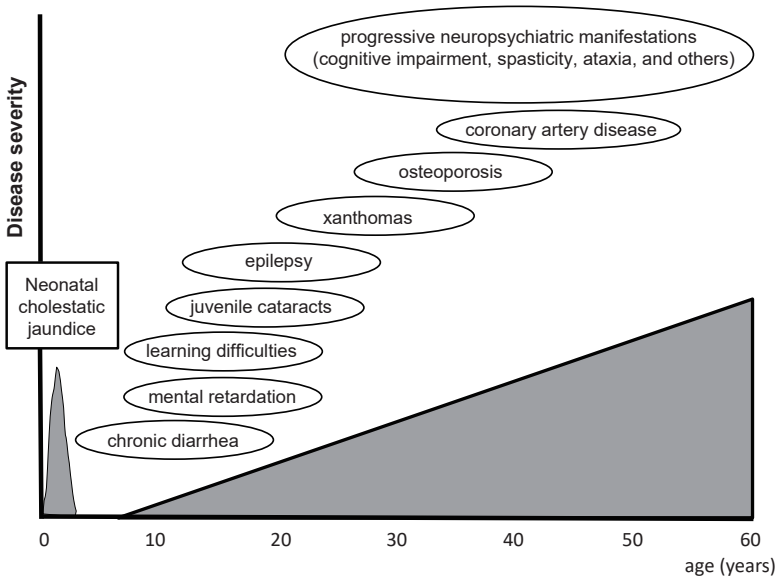

Fig. 2. Representative clinical course of classical form CTX
Figure shows typical ages of onset of CTX-related symptoms.

associated with CTX. Therefore, the diagnostic gold standard is genetic analysis of the *CYP27A1* gene[4, 38]. The diagnosis is confirmed by the presence of biallelic pathogenic *CYP27A1* mutations[4, 38]. To date, over 99 pathogenic mutations, including missense mutations, nonsense mutations, splice-site mutations, and insertion/deletion mutations, have been reported worldwide[6]. A relatively high frequency of *CYP27A1* mutations in particular ethnic groups has been reported: c.1016C>T (p.T339M), c.1183C>T (p.R395C), and c.1263+1G>A in the Netherlands[13], c.646G>C (p.A216P), c.1183C>T (p.R395C), c.1184+1G>A, c.1263+1G>A, and a 1.9 kb deletion including exons 7-9 in Italy[38], c.1183C >T (p.R395C) in northwestern Spain and c.1213C>T (p.R405W) in southern Spain[3], c.1214G>A (p.R405Q), c.1421G>A (p.R474Q), c.435G>T (p.G145=), and c.1420C>T (p.R474W) in Japan[9], which seems to be reasonable considering the allele frequency reported in the ExAC[33]. The allele frequencies of these variants in six global populations according to the ExAC database (version 0.3) are shown in **Supplementary Table 1**. Although no genotype-phenotype correlation has been reported[2, 3, 13], our nationwide survey revealed possible associations between c.1421G>A (p.R474Q) and classical form CTX, c.1241G>A (p.R405Q) and spinal form CTX, and c.435G>T (p.G145=) and non-neurological form CTX despite considerable phenotypic variation among patients with the same genotype[9].

Clinical Features

Clinical Phenotypes

Clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms vary from patient to patient. Systemic symptoms include neonatal jaundice or cholestasis, chronic diarrhea, juvenile cataracts, xanthomas, osteoporosis, and coronary heart disease. The neurological and psychiatric manifestations of CTX vary widely. Intellectual disability as well as pyramidal and cerebellar signs are the most frequent and are cardinal clinical features[2-4, 7, 9]. In addition, CTX patients can present with extrapyramidal manifestations, peripheral neuropathy, epilepsy, and psychiatric disturbances. Autonomic involvement has also been reported[39].

A representative clinical course of classical form CTX, the most common form of this condition, is shown in **Fig. 2**. Patients with classical form CTX develop neuropsychiatric symptoms attributed to the cerebrum, cerebellum, and/or brainstem, in combination with various systemic manifestations. The concept of spinal form CTX, also called spinal xanthomatosis, was proposed by Virrips *et al.* in 1999[40]. Patients exhibit clinical symptoms and signs related to involvement of the corticospinal tracts and dorsal columns of the spinal cord, without intellectual impairment, cerebellar signs, or peripheral neuropathy, at the time of presentation of the spinal cord syndrome[40]. Although most patients with spinal form

CTX also exhibit various systemic and neurological symptoms, spinal form CTX without other neurological manifestations has been reported[41-46]. Spinal form CTX has a relatively mild clinical course compared with classical form CTX[40].

We have proposed non-neurological form CTX[9] as another clinical phenotype. Although patients with the non-neurological form may develop neurological symptoms later in life, two genetically confirmed CTX patients in their fifties showed no evidence of neurological manifestations ≥ 20 years after disease onset. Therefore, we regarded the non-neurological form as a distinct clinical phenotype of CTX[9].

All CTX patients exhibit increased serum cholestanol levels at the time of diagnosis[2-4, 9]. While a significant relationship between serum cholestanol and clinical phenotype or disability was not detected[3], Sekijima *et al.* showed that classical form patients had significantly higher levels of cholestanol than spinal form patients[9].

Systemic Manifestations/Neonatal Jaundice or Cholestasis

Prolonged neonatal jaundice or cholestasis could be the earliest clinical presentation of CTX[47]. Laboratory findings have revealed conjugated hyperbilirubinemia with raised transaminases and alkaline phosphatase, whereas levels of γ-glutamyl transferase were normal or minimally elevated[47-50], which is the characteristic feature of inborn errors of bile acid synthesis[51]. In one study, hepatomegaly or hepatosplenomegaly was evident[50]. Liver biopsy specimens have revealed nonspecific chronic active hepatitis with giant cell transformation, piecemeal or focal bridging necrosis, and fibrosis, in addition to intralobular cholestasis[47-50]. Cirrhosis was detected in an explanted liver[50]. In addition, retrospective cohort studies have demonstrated that about 8–16% of patients had a past medical history of neonatal cholestatic jaundice[4, 13, 47]. Furthermore, family histories have revealed fetal deaths or jaundice-related infantile deaths among siblings of affected individuals[47].

Von Bahr *et al.* described a patient with genetically confirmed CTX who had fatal cholestatic liver damage[48]. Recently, Gong *et al.* reported on eight patients who presented with neonatal cholestasis. Among their cohort, this was fatal in four and one underwent liver transplantation. Although neonatal cholestasis associated with CTX has been generally assessed as transient and self-limiting with patient survival, a substantial proportion of patients could experience a more severe clinical course than previously recognized[50]. The mechanism by which mutations in the *CYP27A1* gene lead to cholestasis may involve nuclear receptors such as farnesoid X receptor (FXR). CDCA is a potent stimulator of FXR[52]. Marked reduction of CDCA in CTX leads to decreased activation of FXR, which results in reduced expression of the bile salt export pump, causing a decrease in canalicular bile salt transportation[48, 52].

Systemic Manifestations/Chronic Diarrhea

Chronic unexplained diarrhea begins in infancy and continues into adulthood[2]. It may be the earliest symptom of CTX and could start within the first year of life[53]. Gastrointestinal tract investigations in patients with diarrhea did not produce any abnormal findings[54]. Also, rectal biopsy did not demonstrate any accumulation of cholestenol or cholesterol and fatty acids could not be detected in the feces[54]. Usually, diarrhea ceases immediately after starting treatment with CDCA[11]. Although the pathogenesis of diarrhea is still unclear, presence of bile alcohol in the lumen of the gut and/or intraluminal deficiency of CDCA are the most likely causes[54].

Systemic Manifestations/Ocular Manifestations

Juvenile cataracts are one of the earliest clinical signs and often precede tendon xanthomas and neurological symptoms, and are usually noted in the second decade of life. Lens nuclei from CTX patients had a greater cholestanol content compared with the senile lens nuclei used as a control[55]. Although stabilization of cataracts with CDCA treatment has been reported[11], complete resolution is unlikely[56] and operations should be considered. Early onset of cataracts is uncommon and therefore, juvenile cataracts are arguably an important cue for early diagnosis of CTX. A screening for CTX among 170 patients with idiopathic bilateral cataracts diagnosed between the ages of 2 and 21 years identified 3 cases[57].

In addition to cataracts, ophthalmological manifestations include optic neuropathy with optic disc paleness, premature retinal vessel sclerosis, and cholesterol-like deposits[58]. Optic neuropathy with features suggestive of optic neuritis has also been reported[59].

Systemic Manifestations/Xanthomas

Xanthomas usually appear during the second or third decade of life. They typically occur on the Achilles tendon, but may be found on the elbow, neck, knee, and the bottom of the foot **(Fig. 3)**. The patellar and finger extensor tendons are also common sites for development of tendon xanthomas[60-64]. Xanthomas in the lung[65] and choroid plexus have also

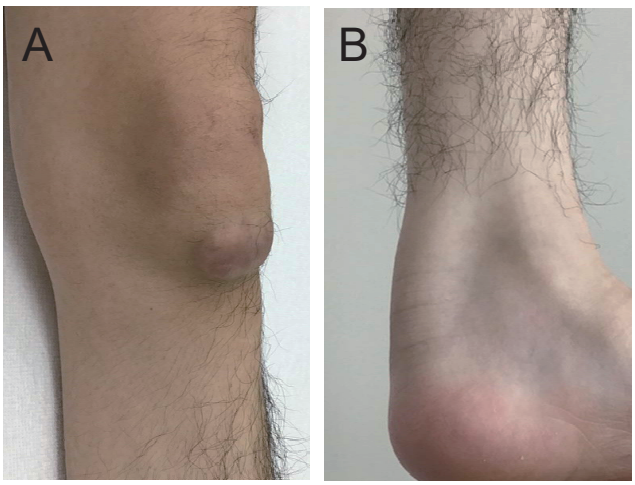

Fig. 3. Xanthomas in a patient with CTX

Figure shows xanthoma on the knee (A) and one on the Achilles tendon (B).

been reported[60, 66, 67]. It is noteworthy that presence of xanthomas is a characteristic feature of the disease, but it is not mandatory for CTX diagnosis[68]. Biopsy specimens of xanthomas show lipid crystal clefts with infiltration of foamy macrophages[64, 69]. In gallium-67 scintigraphy, there can be abnormal uptake in Achilles tendons[70], even if Achilles tendon xanthomas were not evident in a physical examination or on MRI[44]. In addition, positron emission tomography (PET) using ^{18}F-2-deoxy-2-fluoro-glucose (FDG) showed abnormally high radioactivity in the Achilles tendons and adjacent regions[5]. Although CDCA treatment does not significantly reduce tendon xanthomas[10], a decrease in size has been reported in some subjects[71, 72].

Systemic Manifestations/Skeletal System Involvement

Osteoporosis and increased bone fractures are CTX-associated systemic manifestations. However, the underlying pathogenesis of osteoporosis in this condition is still unknown. Decreased levels of serum 25-hydroxyvitamin D were detected in CTX patients[73-75]. In contrast, however, Federico *et al.* reported that levels of 25-hydroxyvitamin D were substantially within the normal range[76], indicating that a deficiency in vitamin D metabolites may not be the only factor responsible for the development of osteoporosis in CTX[74]. An alternative hypothesis for explaining the cause of osteoporosis is impairment of intestinal calcium absorption due to changes in the quantity and composition of bile acids[76]. In general, osteoporosis has been considered to occur in the later stages of the disease[4, 9]. However, teenage CTX patients could have early osteoporosis and a history of bone fracture[77]. CDCA treatment has been shown to improve bone mineral density (BMD)[74, 76].

Skeletal deformities including kyphosis, pectus excavates, pes equinovarus, and pes cavus were found in CTX patients[77] and Ginanneschi *et al.* reported that pes cavus occurrence was not significantly different in groups with and without peripheral nerve abnormalities[78].

Systemic Manifestations/Cardiovascular System Involvement

Premature atherosclerosis and cardiovascular disease have been reported as systemic manifestations in CTX patients even in their thirties[79-82]. Myocardial infarction is a cause of premature death in this condition[82]. Kuriyama *et al.* reviewed 144 cases of CTX and reported that 15 patients (10.4%) had cardiovascular disease, consisting of coronary artery disease in ten patients, ischemic changes on electrocardiogram in four, and mitral valve insufficiency in one patient[79]. Coronary artery disease was evident in 8 of 40 CTX patients (20%) in a nationwide survey on CTX in Japan[9]. In this survey, the mean age at onset of coronary artery disease was 52.5. ± 5.8 years (mean ± standard deviation (SD))[9]. Duell *et al.* reported that 3 of 43 CTX patients (7%) had premature cardiovascular disease, consisting of myocardial infarction in two patients, and angina pectoris in one patient in the USA[8]. Abdominal aortic aneurysm, coronary artery dissection, aneurysmal coronary artery disease, advanced carotid atherosclerotic lesions, and thickening of the interatrial septum compatible with lipomatous hypertrophy have also been reported in CTX [81, 83-86].

Systemic Manifestations/Pulmonary Involvement

Elevated levels of cholestanol in bronchoalveolar lavage fluid as well as in serum have been reported in CTX patients without pulmonary symptoms, or radiological and pulmonary function abnormalities. Transbronchial lung biopsy specimens have revealed foamy macrophages and small granulomas in alveolar septa[87].

Neuropsychiatric Manifestations/Intellectual disability

Among CTX patients, 48–74% present with intellectual disability[2-4, 9], which is one of the most frequent neurological symptoms. It is particularly important to take developmental delays, mental retardation, and learning difficulties beginning in childhood into consideration for early diagnosis of CTX[2-4, 7, 9, 53]. Cognitive decline, presenting in adolescence or early adulthood, is also frequently observed[2, 3, 9]. Although a neuropsychological profile

of patients with CTX remains undetermined, a fronto-temporal dementia phenotype exhibiting behavioral and personality changes[88], extensive cerebral cortex symptoms including left-right disorientation, constructional apraxia, and temporal and spatial disorientation in addition to frontal lobe dysfunction[89], and a corticobasal syndrome phenotype[90] have been reported.

Neuropsychiatric Manifestations/Pyramidal and Cerebellar Signs

Pyramidal and/or cerebellar signs typically emerge in the third or fourth decade and lead to gait disturbance in CTX patients[2, 4, 9]. Pyramidal and cerebellar signs have been detected in 64–92% and 36–83% of patients with CTX, respectively[2-4, 9]. Pyramidal signs such as spasticity, hyperreflexia, and extensor plantar response can be cardinal clinical signs especially in patients with spinal form CTX[40-46]. Owing to dorsal column involvement, simultaneous occurrence of impaired position and vibration sensation in the lower extremities can lead to spastic-ataxic gait in this form[41, 45]. Mignarri *et al.* have reported the usefulness of transcranial magnetic stimulation in detecting corticospinal tract damage[91]. Cerebellar signs include nystagmus, ataxic dysarthria, as well as limb and truncal ataxia[69, 92-94]. Pyramidal signs frequently coexist with cerebellar signs[2, 3].

Neuropsychiatric Manifestations/Extrapyramidal Manifestations

CTX patients can present with a wide range of movement disorders including parkinsonism[90, 95, 96], dystonia[97-99], myoclonus[98, 100, 101], and postural tremor[100, 102]. When movement disorders are diagnosed, patients have a tendency to present with other CTX-associated systemic and neuropsychiatric manifestations[103]. Parkinsonism usually occurs later in life[7, 95, 103] and is the most frequently reported type of movement disorder in CTX, followed by dystonia, myoclonus, and postural tremor[103]. Parkinsonism seems to be a treatment-resistant feature in CTX[13], with CDCA treatment seemingly having no effect. In addition, CTX patients may develop parkinsonism during treatment with CDCA[103]. The effect of L-dopa is controversial[90, 95, 103-105]. In addition to the characteristic brain MRI findings of CTX, signal hyperintensities on T2-weighted images in the substantia nigra, globus pallidus, and striatum [90, 95, 96, 103] have been described and functional dopaminergic imaging has demonstrated a pre-synaptic dopaminergic deficit in CTX patients presenting with parkinsonism[90, 95, 96, 104, 105]. Although movement disorders are considered a late disease manifestation, Zubarioglu *et al.* reported that all six patients who were diagnosed before 18 years of age had intention tremor[77].

Neuropsychiatric Manifestations/Peripheral Nervous System Involvement

Peripheral neuropathy is an established clinical feature of CTX; however, it is still being debated whether the underlying pathogenesis of CTX-related polyneuropathy is demyelinating or axonal in origin. Based on the presence of onion bulbs, which are generally considered a hallmark of chronic demyelination, the pathological process has been interpreted as demyelinating[106, 107]. On the other hand, Verrips *et al.* reported that axonal degeneration was the predominant process on the basis of nerve conduction velocity (NCV) studies and sural nerve biopsy specimens showing features of axonal degeneration[108]. In addition to axonal polyneuropathy and demyelination polyneuropathy, a mixed type of neuropathy has been reported, indicating that CTX could exhibit any type of neuropathy[109]. CTX-related polyneuropathy seems to be predominantly motor neuropathy[78, 109]. Although neurophysiologically confirmed neuropathy frequently occurs in CTX, signs and symptoms related to polyneuropathy are often absent or difficult to appreciate because central nervous system involvement may dominate the clinical picture[4, 78, 109]. The disease severity of polyneuropathy varies greatly among patients, ranging from asymptomatic presentations to severe polyneuropathy[78, 109, 110]. Thickening of the nerve roots and trunks of the lumbosacral plexus or cauda equina has been reported[90, 111].

Neuropsychiatric Manifestations/Muscle Involvement

Controversy exists regarding whether muscle involvement is a characteristic feature in CTX. Federico *et al.* noted mild myopathic changes[112], while Verrips *et al.* reported that muscle biopsies demonstrated neurogenic changes without any definite myopathic characteristics[108]. The results for mitochondrial respiratory chain enzymatic activity are also controversial[108, 113]. Abnormal findings from ultrastructural studies of muscles include changes in the mitochondria and membranous system, and an increased amount of lipid droplets, lipofuscin, and glycogen; however, the significance of these findings remains to be determined[39, 108, 112].

Neuropsychiatric Manifestations/Epilepsy

In CTX, 10–33% of patients have epileptic seizures[2-4, 7, 9]. Epilepsy can develop at any stage in life and is often seen in the early phase of the disease[7].

Epilepsy could be a diagnostic cue in some cases[114-116]. A CTX patient presenting with infantile spasms has also been reported, but this is a rare case[117]. Electroencephalographic abnormalities are frequently observed in cases of CTX even without clinical signs of seizures[11, 118]. In addition to slow background activity composed of theta and delta waves, bursts of high voltage slow activity are frequently demonstrated. Spike and sharp wave complexes can also be detected[10, 11, 118]. CDCA treatment leads to improvement or normalization of electroencephalographic findings[10, 11, 60, 118], and epilepsy in CTX seems to respond well to anti-epileptic agents[12, 114-116, 119]. CDCA treatment could lead to improved seizure control[12, 60, 120], even in patients with drug-resistant epilepsy[121].

Neuropsychiatric Manifestations/Behavioral manifestations

Psychiatric and behavioral manifestations include personality changes with irritability and aggressivity, depression, delusional syndrome, catatonia, psychosis, attention-deficit hyperactivity disorder, oppositional-defiant disorder, and autism spectrum disorder[13, 122]. Behavioral disorders and affective/mood disorders associated with learning difficulties or mental retardation appearing during childhood or adolescence should lead to biochemical investigations to exclude CTX.

Radiological, Pathological, and Neurophysiological Examinations

Neuroimaging

The most distinctive neuroradiological findings are signal hyperintensities on T2-weighted and/or FLAIR images in the dentate nuclei and adjacent cerebellar white matter[123, 124]. Abnormal signal changes in the dentate nuclei can be more clearly detected on FLAIR images than on T2-weighted images[123]. It was found that abnormal hyperintensities on T2-weighted and/or FLAIR images could be detected in the globus pallidus, internal capsule, substantia nigra, cerebral peduncles, inferior olive, and periventricular white matter, with a tendency to spare the U-fibers and corpus callosum[125]. Supratentorial and/or infratentorial atrophy are also observed[123, 124, 126] **(Fig. 4)**. Cortical volume, rather than white matter volume, was correlated with clinical status and cortical atrophy could be detected in all neocortical regions, with a preference for the fronto-parietal cotrtex[126]. In addition, cerebellar vacuolation, which is detected as hypointense lesions on both T1-weighted and FLAIR images, has been recently indicated as a marker of a poor prognosis in CTX[127, 128], while absence of dentate nuclei signal alteration is considered an indicator of a better prognosis[128]. Furthermore, calcifications were detected in the dentate nuclei in a subgroup of patients[128] and the hot cross bun sign in the pons, a characteristic finding of multiple system atrophy, has been reported[69].

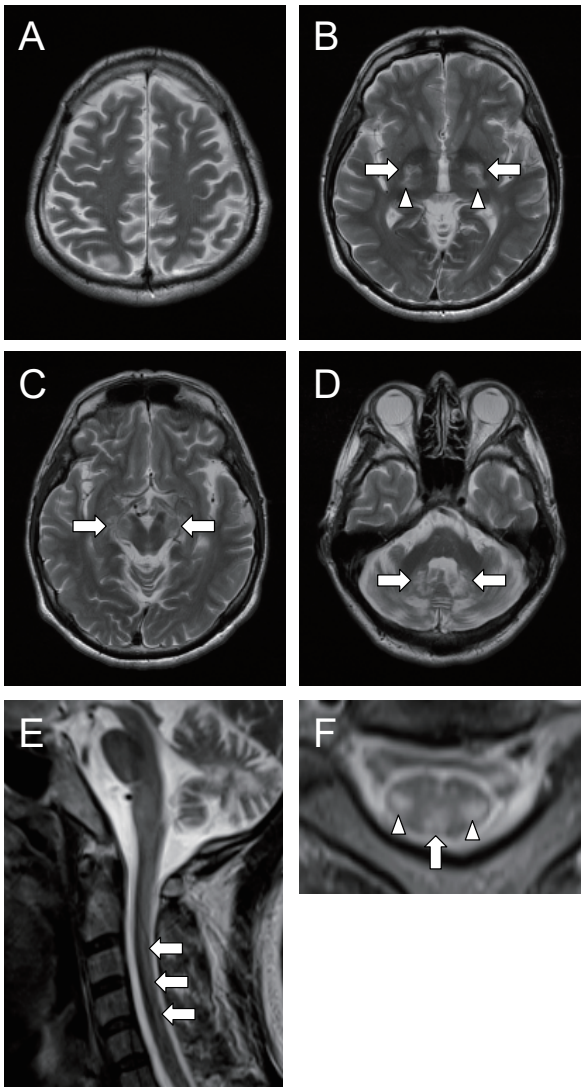

Fig. 4. Brain magnetic resonance imaging (MRI)

Axial T2-weighted images of the brain showing abnormal hyperintensities in the globus pallidus (arrows in B), internal capsules (arrowheads in B), cerebral peduncles (arrows in C), and dentate nuclei (arrows in D). Diffuse cerebral (A) and cerebellar (D) atrophy are evident. Sagittal T2-weighted image of the spinal cord exhibiting longitudinally extensive hyperintense lesions (arrows in E). Axial T2-weighted image at the C3 level showing involvement of lateral corticospinal tracts (arrowheads in F) and gracile tracts (arrow in F).

In patients with spinal cord involvement, a spinal cord MRI demonstrated longitudinally extensive

hyperintense lesions involving lateral corticospinal tracts and gracile tracts on T2-weighted images[40, 44-46]. It is noteworthy that absence of signal changes on spinal cord MRI cannot rule out the possibility of spinal form CTX[42, 43].

On magnetic resonance spectroscopy (MRS), decreases in N-acetylaspartate (NAA) intensities and increases in lactate signals point to axonal damage and brain mitochondrial dysfunction, respectively[123]. In addition to decreased NAA intensities, lipid peaks were evident on MRS using a short TE[129]. Increased levels of myo-inositol indicate gliosis and astrocytic proliferation[129, 130].

Cerebellar glucose hypometabolism in ^{18}F-2-deoxy-2-fluoro-glucose positron emission tomography (FDG-PET) and cerebellar hypoperfusion in single photon emission computed tomography (SPECT) with ^{99m}Tc-ethylcysteinate dimer (ECD) have been reported despite normal cerebellar morphology[88, 131, 132]. In addition to in the cerebellum, SPECT using ^{99m}Tc-ECD and ^{123}I-*N*-isopropyl-*p*-iodoamphetamine (^{123}I-IMP) revealed cerebral hypoperfusion, predominantly in the fronto-parietal lobes[88, 89, 132]. Gray matter atrophy patterns were correlated with hypoperfusion in SPECT using ^{99m}Tc- ECD[133].

Diffusion tensor imaging (DTI) revealed that fractional anisotropy (FA) reduction preceded structural alterations detected by voxel-based morphometry and correlated with cognitive function[133]. Widespread reductions of FA and decreased track-density were demonstrated[120, 134].

Neuropathology

At macroscopic examination, nonspecific brain and cerebellar atrophy and a yellowish soft tissue in the cerebellum, cerebrum, choroid plexus, cerebral peduncles, and globus pallidus were observed[135-138]. In the cerebral peduncles, cystic necrosis of the corticospinal tracts has been reported[139]. Microscopic examinations have revealed lipid crystal clefts, neuronal loss, demyelination, reactive astrocytosis, and foamy macrophages in the affected regions, especially in the dentate nucleus and surrounding area, as well as in the cerebrum, basal ganglia, brainstem, and, spinal cord[65, 124, 135-139]. In patients with spinal cord involvement, extensive symmetric loss of myelin and axons was detected particularly in the lateral corticospinal tracts and gracile tracts of the spinal cord[40].

Neurophysiological Examinations

In addition to NCV studies and electroencephalography, abnormalities have been found in neurophysiological examinations. The P100 peak latency of visual evoked potentials (VEPs) was delayed[109, 140, 141] and the Ⅰ to Ⅲ, Ⅲ to Ⅴ, and Ⅰ to Ⅴ interpeak latencies of brain stem evoked potentials (BAEPs) were prolonged[109, 140, 141]. Central conduction time in somatosensory evoked potentials (SSEPs)[109, 142] and motor evoked potentials (MEPs)[89, 91, 141] were increased, with lower extremity predominance.

Diagnosis

Importance of Early Diagnosis and Treatment

CTX is a treatable metabolic disorder; however, once significant neurological symptoms are established, clinical deterioration can occur despite normalization of cholestanol levels after treatment with CDCA[3]. Even with therapy, only 28% of the patients remained stable, whereas 60% continued to deteriorate and 20% died, in a cohort of 25 patients with CTX in Spain[3]. Duell *et al.* reported that clinical deterioration during follow up was observed in patients who had significant neurological symptoms when they were diagnosed at the age of 25 years or older[8]. Yahalom *et al.* and Stelten *et al.* have shown that the age of diagnosis and initiation of CDCA treatment correlates with the prognosis of patients with CTX[12, 13]. Berginer *et al.* reported two siblings with CTX who began CDCA treatment from 2 and 7 years of age, respectively, and did not develop any neurological manifestations during a 14-year follow-up period[142]. These findings strongly suggest that early diagnosis and treatment are crucial in CTX. However, retrospective cohort studies on CTX have revealed a substantial diagnostic delay of 15–25 years[2-4, 9].

Juvenile cataracts are usually the earliest clinical sign that precedes tendon xanthomas and neurological symptoms. Cruysberg *et al.* emphasized that the combination of juvenile cataracts and chronic diarrhea is noteworthy in the early diagnosis of CTX[143]. It is recommended that all patients with cataracts before the age of 30 years are screened for CTX, especially if they also have CTX-related conditions such as chronic diarrhea, tendon xanthomas, and/or neuropsychiatric symptoms[8]. Verrips *et al.* emphasized that presence of tendon xanthomas is not obligatory for a diagnosis of CTX and recommended that presence of two of the four clinical features of premature cataracts, intractable diarrhea, progressive neurological signs and symptoms, and tendon xanthomas prompt thorough biochemical screening for CTX[68]. It is also important to consider intellectual disability, usually presenting at school age, for early diagnosis of CTX[4]. In addition, because affected relatives may be asymptomatic, biochemical examination of all siblings of a patient with CTX is recommended[2, 4].

Table 1. Diagnostic criteria for cerebrotendinous xanthomatosis (Sekijima *et al.*[9])

A. Symptoms
1. Tendon xanthoma
2. Progressive neurological dysfunction[a] or mental retardation
3. Juvenile cataract
4. Juvenile coronary artery disease
5. Chronic unexplained diarrhea
6. Juvenile osteoporosis
7. Prolonged neonatal cholestasis
B. Biochemical finding
Elevated serum cholestanol level
C. Genetic testing
Pathogenic mutation in *CYP27A1* gene (homozygosity or compound heterozygosity)
D. Differential diagnosis
Increased serum cholestanol level due to following diseases should be excluded
· Familial hypercholesterolemia
· Sitosterolemia
· Obstructive biliary tract disease
· Hypothyroidism
Diagnostic category
Definite: At least one of symptom in A and B+C+D
Probable: At least one of symptom in A and B+D
Possible: At least one of symptom in A and B

[a] Representative progressive neurological dysfunction includes cognitive dysfunction, cerebellar symptoms, pyramidal symptoms, extrapyramidal symptoms, seizure, peripheral neuropathy, and sensory disturbance attributed to spinal cord.

To identify and treat CTX patients at an initial stage of the disease, Mignarri *et al.* created a suspicion index and developed a diagnostic algorithm for early diagnosis of CTX[4]. Their suspicion index comprised weighted scores assigned to indicators such as family history characteristics and common systemic and neurological symptoms. They suggested that their proposed algorithm would be useful for early diagnosis, even in patients before the onset of disabling neurological symptoms including ataxia, spasticity, and psychiatric disturbances[4].

Diagnostic Criteria

In the absence of generally accepted diagnostic criteria for CTX, we recently proposed new diagnostic criteria with emphasis on early diagnosis **(Table 1)**[9]. They include clinical symptoms, biochemical findings, genetic analysis, and differential diagnosis. We established three diagnostic categories in accordance with levels of certainty: definite, probable, and possible CTX. The diagnosis of possible CTX is made when there is at least one CTX-related clinical symptom and elevated levels of serum cholestanol (≥ 4.5 μg/mL, mean ± SD: 2.35 ± 0.73 μg/mL). Excluding other conditions with elevated levels of cholestanol is necessary for diagnosis of probable CTX. A definite diagnosis of CTX is confirmed by the presence of biallelic mutations in the *CYP27A1* gene.

Differential Diagnosis

Differential diagnosis of CTX differs substantially according to presenting symptoms. Inborn errors of bile acid metabolism including CTX lead to neonatal cholestasis or hepatitis[144, 145], which can be the first manifestation in this disease. In patients with juvenile bilateral cataracts and/or progressive mental deterioration, CTX should be considered[2, 57]. When xanthomas are evident, differential diagnosis includes familial hypercholesterolemia (FH) and sitosterolemia. FH is characterized by elevated levels of LDL cholesterol, the presence of tendon xanthomas, and premature coronary artery disease, and mutations in *LDLR*, *APOB*, and *PCSK9* have been reported to cause FH[146]. Sitosterolemia is an autosomal recessive sterol storage disorder characterized by elevated levels of LDL cholesterol and plant sterols such as sitosterol and campesterol, tendinous and tuberous xanthomas, and premature atherosclerosis. It is caused by biallelic mutations in either *ABCG5* or *ABCG8*[147]. The presence of juvenile cataracts, chronic unexplained diarrhea, and progressive neuropsychiatric manifestations can distinguish CTX from these two disorders. Other

conditions with elevated levels of cholestanol include obstructive biliary tract diseases and hypothyroidism. In patients with cerebellar ataxia, CTX patients might be misdiagnosed as spinocerebellar atrophy, multiple system atrophy, or Marinesco-Sjögren syndrome[68]. CTX should be included in the differential diagnosis of spastic paraplegia[42, 44].

Clinical Management

CDCA has been approved as first-line treatment for CTX. In a landmark study published in 1984, Berginer *et al.* demonstrated the long-term efficacy of oral CDCA treatment[10]. In addition to a decrease in serum cholestanol and elimination of abnormal urinary and biliary excretion of bile alcohols, CDCA treatment led to an improvement in electroencephalographic findings and neurological manifestations including intellectual impairment, pyramidal and cerebellar signs, and peripheral neuropathy[10, 11]. CDCA treatment is recommended at a dose of 750 mg/day for adults and 15 mg/kg/day for children in three divided oral doses[10, 11]. It has been shown to result in a gradual decline in serum cholestanol during the first 2 years[148, 149]. Assessment of cholestanol levels may be useful in monitoring patient adherence to treatment. However, it should be noted that a decreased level of cholestanol does not necessarily suggest a good prognosis[3]. In Japan, CDCA has been approved for dissolution of gallstones, but not for the treatment of CTX.

Although CDCA is a relatively safe drug, gastrointestinal manifestations and drug-induced liver damage may occur[44, 60, 150]. Huidekoper *et al.* reported an infantile patient with CTX who developed jaundice with hepatomegaly within 6 weeks after initiating CDCA administration at a dosage of 15mg/kg/day[151]. After treatment with CDCA was stopped, liver size and function rapidly normalized. CDCA supplementation was then restarted and maintained at 5 mg/kg/day with no further evidence of liver dysfunction and adequate metabolic control. Duell *et al.* reported that 9% of patients required dose adjustment for CDCA owing to moderate drug-induced liver damage[8]. These findings suggest that clinical and laboratory monitoring and dosage adjustment for CDCA are essential in the treatment of CTX, especially in infants and young children[8, 151].

CDCA was initially preferred to cholic acid because it was more effective in reducing cholesterol 7α-hydroxylase and had a stronger negative feedback effect on it[127, 152]. Cholic acid has been shown to be effective in the treatment of other genetic defects in bile acid synthesis[153]. Since CDCA is intrinsically hepatotoxic, cholic acid is considered the safer option in CTX, especially in infancy[49]. Mandia *et al.* reported potential efficacy for cholic acid in adult patients with CTX, including individuals whose CDCA treatment was discontinued due to supply difficulties[127]. Treatment with cholic acid not only significantly reduced cholestanol levels in all patients but also led to improvement or stabilization of systemic and/or neurological manifestations[127]. No adverse effects were reported in patients undergoing cholic acid treatment, suggesting that cholic acid may be a suitable alternative treatment, especially in patients with adverse effects related to CDCA, such as drug-induced liver damage[60, 127].

Treatment with ursodeoxycholic acid, which does not inhibit cholesterol 7α-hydroxylase, has been shown to be ineffective[10, 154]. When ursodeoxycholic acid was substituted for CDCA, plasma cholestanol returned to pretreatment levels[10].

The effectiveness of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins) remains controversial. Lewis *et al.* reported that mevinolin normalized serum cholestanol and reduced the size of xanthomas[155], whereas Batta *et al.* found that lovastatin did not affect abnormal bile acid synthesis or reduce plasma cholestanol levels[154]. Although synergistic effects of combination therapy with CDCA and HMG-CoA reductase inhibitors on serum cholestanol or urine bile alcohols have been observed[71, 81, 149], absence of an additive effect has also been reported[148]. After switching from combined therapy of CDCA and HMG-CoA reductase inhibitors to HMG-CoA reductase inhibitor monotherapy, clinical symptoms such as xanthomas and neurological manifestations, and electroencephalographic findings were re-exacerbated with reappearance of abnormal bile alcohol excretion or elevated plasma cholestanol [71, 156]. Therefore, HMG-CoA reductase inhibitors could be beneficial when combined with CDCA, but long-term clinical benefits should be proven.

Low-density lipoprotein (LDL) is a major carrier of serum cholestanol. LDL-apheresis, usually combined with CDCA and HMG-CoA reductase inhibitors, has been performed to reduce serum cholestanol[157-160] Levels of serum cholestanol or 7α -hydroxy-4-cholesten-3-one decreased after each LDL-apheresis, but returned to their initial levels within 1–2 weeks[159, 161], suggesting that LDL-apheresis at a frequency of at least once every 2 weeks is necessary. The effects of LDL-apheresis on clinical manifestations are still controversial despite the decrease in cholestanol. In addition, the invasiveness of this procedure and its necessity for the long-term management of the disease should be taken into

account[161].

Symptomatic treatments for epilepsy[115, 120], psychiatric manifestations[122], and movement disorders such as dystonia[97, 98] and parkinsonism[90, 95] should be considered. Cataract extraction is also usually required[57].

After treatment with CDCA, improvements in neurophysiological examinations including NCV studies[78], VEP[72, 78], SSEP[72], MEP[72, 91], and EEG[10, 11] have been reported. Besides conventional MRI, DTI and tractography, MRS, and SPECT imaging might have potential as neuroimaging modalities for monitoring treatment response[120, 132-134, 162, 163].

Conclusions and Perspectives

CTX is considered a rare inherited metabolic disorder. However, it may be under- or misdiagnosed, although effective treatment is available. There is a crucial "point of no return" in CTX, after which treatment initiation can no longer prevent the progression of the disease[12]. The earlier the diagnosis is made and the sooner treatment is started, the more likely it is that the significant neurological manifestations that diminish the quality of life of patients with CTX can be improved or even prevented. Neonatal jaundice, chronic unexplained diarrhea, developmental delays, mental retardation, and learning difficulties are non-specific symptoms, but they could be diagnostic cues for pediatricians. Ophthalmologists have an opportunity to diagnose CTX, because bilateral cataracts are one of the earliest clinical symptoms and juvenile-onset bilateral cataracts could be useful as a screening marker for CTX[57]. Furthermore, it could be beneficial to screen newborns for CTX in the future[164].

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Supplementary Table 1. Allele frequencies of *CYP27A1* variants according to Exome Aggregation Consortium database (version 0.3)

variant	AFR	AMR	EAS	FIN	NFE	SAS
p.G145=	0.00000	0.00000	0.00040	0.00000	0.00000	0.00000
p.A216P	0.00000	0.00000	0.00000	0.00000	0.00004	0.00000
p.T339M	0.00000	0.00000	0.00010	0.00000	0.00002	0.00007
p.R395C	0.00010	0.00020	0.00000	0.00030	0.00020	0.00006
p.R405W	0.00000	0.00009	0.00000	0.00000	0.00000	0.00006
p.R405Q	0.00010	0.00009	0.00050	0.00000	0.00004	0.00000
p.R474W	0.00000	0.00000	0.00000	0.00000	0.00002	0.00000
p.R474Q	0.00000	0.00000	0.00010	0.00000	0.00002	0.00000
c.1184+1G>A	0.00000	0.00000	0.00000	0.00000	0.00006	0.00070
c.1263+1G>A	0.00000	0.00009	0.00010	0.00000	0.00007	0.00000

AFR: African; AMR: Admixed American; EAS: East Asian; FIN: Finnish; NFE: Non-Finnish European; SAS: South Asian.