

# Ophthalmologists and Cerebrotendinous Xanthomatosis (CTX): *Making the Diagnosis*

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## IN THIS ISSUE

### INTRODUCTION

### CASE PRESENTATION

### MAKING A DIAGNOSIS

- Gastrointestinal Clinical Manifestations
- Ocular Clinical Manifestations
- Metabolic Clinical Manifestations
- Neurologic Clinical Manifestations
- Other Clinical Manifestations
- Laboratory Findings

### DIAGNOSTIC TOOL

### DIFFERENTIAL DIAGNOSIS

### DISCUSSION: IMAGING

### CONCLUSIONS

## INTRODUCTION

A patient presenting with bilateral juvenile cataracts may be spared a lifetime of not only visual disability but also extra-ocular disability by an alert pediatric ophthalmologist who sees beyond the obvious. Ophthalmologists should ask the parents of all pediatric patients with bilateral cataracts a few simple questions to determine whether the child should have a workup for cerebrotendinous xanthomatosis (CTX), an underdiagnosed lipid storage disease associated with progressive neurologic dysfunction.<sup>1</sup> Because bilateral cataracts are an almost universal symptom in patients who have early onset of CTX,<sup>2</sup> the pediatric ophthalmologist is in a unique position to identify and diagnose CTX at a time when serious disability can be prevented. Otherwise, patients often go years or decades without receiving a diagnosis and lose the window of opportunity to prevent irreversible neurologic damage.

During childhood, the typical clinical characteristics of CTX are bilateral cataracts and infantile-onset chronic diarrhea, so the presence of both of these problems in early childhood should raise suspicion and trigger further investigation. Other clinical manifestations of CTX include tendon xanthomas, which generally have their onset in adolescence or young adulthood, and cognitive impairment, psychiatric symptoms, and neurologic disorders that can appear either early or late in the course of the disease, but usually do not appear until adulthood.<sup>1</sup>

CTX is inherited in an autosomal recessive manner, caused by mutations in the *CYP27A1* gene. More than 50 different mutations have been identified.<sup>3</sup> The *CYP27A1* gene is responsible for producing an enzyme called sterol 27-hydroxylase, which works in the pathway that breaks

down cholesterol to form the bile acids necessary for the body to digest fats. In particular, sterol 27-hydroxylase mutations damage the body's capacity to break down cholesterol to a bile acid called chenodeoxycholic acid. Consequently, plasma cholesterol levels remain normal while there is a significant increase in levels of bile alcohols and levels of cholestanol, a byproduct of abnormal bile acid synthesis. The bile alcohols are excreted in bile, urine, and feces, but cholestanol accumulates, especially in the brain, peripheral nerves, lenses, and tendons, and causes the signs and symptoms of CTX.<sup>3</sup>

At least 425 cases of CTX have been published worldwide between 1937 and 2012,<sup>4</sup> but the true prevalence is not definitively known. After encountering a white woman who was homozygous for *CYP27A1* mutation R362C, a US research team conducted a genetic analysis of 115 white volunteers, aged >60 years, who had no personal or family history of neurologic disease.<sup>5</sup> Despite the small size of this pool of subjects, the researchers found one person who was heterozygous for the same gene mutation. Thus they calculated that, among white people, the prevalence of CTX due to homozygosity of *CYP27A1* mutation R362C is ~1.9 per 100,000. However, because there are so many other *CYP27A1* mutations, they estimated that the prevalence of CTX among whites may be several times higher, 3 to 5 per 100,000 people.

According to that estimate, there would be 8400 to 14,000 individuals with CTX in the United States alone,<sup>5</sup> a range that contrasts starkly with the ~400 cases reported worldwide.<sup>4</sup> Clearly, CTX is underdiagnosed.

## CASE PRESENTATION:

March 3, 2004

“Betty\*,” a 10-year-old girl, presented for evaluation of bilateral cataracts and strabismus after seeing a local optometrist. Examination had been normal, with 20/20 vision in each eye, 19 months prior. The patient reported feeling that her vision had decreased over the previous few months. Examination revealed that her current vision was 20/80 in each eye, corrected to 20/60 in the right eye and with no change (20/80) in the left. A cataract with diffuse snowflake-like cloudy vacuoles with posterior subcapsular change was detected in each eye (**Figure 1**). The examination also revealed 18 prism diopters of exophoria at near (likely caused by some difficulty with fusion due to dense cataracts) with 80 arc seconds of stereopsis. Otherwise, the examination was normal, with no evidence of intraocular inflammation.

On questioning Betty’s medical history, her mother said that Betty had been carried to full term, and the pregnancy and birth had been uncomplicated. However, she added that ever since birth, Betty has had diarrhea in excess of 6 loose stools per day, and she was told that her daughter had an “irritable bowel.” Betty was seen by several pediatric gastroenterologists and was currently taking loperamide. At age 6 years, Betty had required hospitalization for dehydration. No endoscopy had been performed, and the opinion, according to her mother, was that Betty had irritable bowel or an unknown parasitic infection. Tests for sprue and malabsorption syndromes were reportedly normal. An unremarkable workup by an allergist had been performed. Also, Betty had a history of several episodes of canker sores.

Betty’s mother described her as a very verbal child and early reader who was able to entertain adults with her precocious language skills from a young age, but had difficulty progressing in math. These observations were considered highly suggestive of nonverbal learning disorder.

Examination of the eyes of both parents showed no cataracts. Based on Betty’s diarrhea, cataracts, and learning problems, she was referred to a metabolic geneticist for evaluation before cataract surgery was scheduled.

*\*The patient’s name has been changed to ensure anonymity.*

**FIGURE 1. Bilateral cataracts in case patient at initial presentation.**



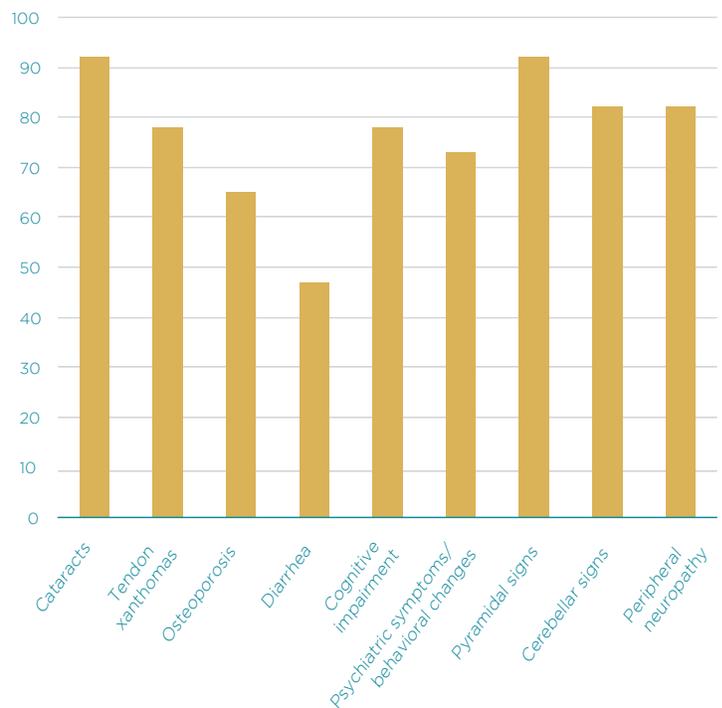
Courtesy of Charles J. Bock, MD

## MAKING A DIAGNOSIS

There is considerable variation among patients with CTX with respect to age at disease onset, systemic involvement, and degree of neurologic impairment.<sup>6</sup> Even within families, the variability in clinical presentation can be considerable. In a series of 49 patients with CTX who were members of 36 unrelated families, cataracts were found in 92% of patients, tendon xanthomas in 78%, osteoporosis in 65%, and diarrhea in 47%.<sup>1</sup> In addition, cognitive impairment was detected in 78% of patients, and psychiatric symptoms and behavioral changes were present in 73%. Pyramidal signs were seen in 92% of patients and cerebellar signs in 82%. Eighty-two percent of patients had peripheral neuropathy (**Figure 2**).<sup>1</sup>

**FIGURE 2. Clinical manifestations in 49 patients with cerebrotendinous xanthomatosis.<sup>1</sup>**

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The signs and symptoms of CTX are many and varied, but being aware of the hallmark features should raise suspicion of the disease and will significantly help the ophthalmologist in making the diagnosis.

### Gastrointestinal Clinical Manifestations

The first systemic manifestation of CTX is often chronic diarrhea that begins when the affected individual is still an infant.<sup>1</sup> This may occur in up to half of all patients and results in frequent visits to pediatricians. In addition, studies have shown that patients with CTX have an increased incidence of prolonged unexplained neonatal cholestatic jaundice.<sup>6</sup>

### Ocular Clinical Manifestations

What generally arouses suspicion of CTX is childhood-onset bilateral cataracts, which usually develop in the first decade of life.<sup>1</sup> Pediatric bilateral cataracts are an almost universal

characteristic of CTX, occurring in up to 85% of patients, and are relatively rare in the general population. Patients develop irregular cortical opacities, anterior polar cataracts, or dense posterior subcapsular cataracts, and these have been reported in ages as young as 5 to 6 years.<sup>7</sup>

In a cohort of more than 2.6 million Danish children who were followed over a 20-year period (until the first diagnosis of cataract, or until death, emigration, 18th birthday, or December 31, 2000, whichever occurred first), the cumulative risk of childhood cataract was only 92.4 per 100,000 children (1995-2000), and this number included those with congenital or traumatic cataracts.<sup>8</sup> Therefore, when a child presents with unexplained cataract, especially bilateral cataracts, CTX should be considered in the differential diagnosis.

Juvenile bilateral cataracts in CTX tend to have a particular morphology that should raise suspicion for the diagnosis when present.<sup>2</sup> Fleck lenticular deposits may be an early sign of CTX, according to a prospective case series that describes 4 siblings and their parents.<sup>2</sup> CTX was first considered when 2 sisters with a history of juvenile cataract were referred for ophthalmologic evaluation. One of the sisters, 22 years old with 20/30 visual acuity in either eye, had undergone bilateral cataract surgery at age 9 years. Preoperative examination had been noteworthy for bilateral fleck opacities throughout the lenses and posterior capsular cataract (best corrected visual acuity, 20/400 in either eye). Lens opacities had previously been diagnosed in the woman's 14-year-old sister, who reported progressively decreasing visual acuity over the past 7 years. Examination revealed bilateral fleck opacities throughout the lens and posterior capsular cataract (best corrected visual acuity, 20/200 in either eye). A brother, 8 years old at the time of initial examination, had no vision impairment but had the same type of fleck deposits bilaterally, although with minimal posterior capsular opacity. Two years later, he was found to have posterior and anterior capsular opacity and reduced visual acuity. Both parents, who were first cousins, had a few similar flecks localized at or near the anterior Y-suture, but they did not have vision symptoms. A fourth sibling did not have flecks, cataracts, or vision impairment when examined at age 6 years. On questioning, the parents said the 3 siblings who presented with fleck deposits had all experienced recurrent intractable diarrhea in early childhood. Genetic testing showed homozygosity for a *CYP27A1* mutation in the 3 siblings with the vision symptoms, heterozygosity for the same mutation in the parents, and no mutation in the child who did not have flecks or other symptoms. Both parents as well as all siblings were asymptomatic.

### **Metabolic Clinical Manifestations**

Tendon xanthomas appear later, usually in the second or third decade, and in patients with CTX classically occur on the Achilles tendon (**Figure 3**).<sup>9</sup> However, xanthomas can also occur on the extensor tendons of the elbow and hand, the patellar tendon, and the neck tendons. While not specific for CTX, as they can occur in association with familial hypercholesterolemia and sitosterolemia, the presence of tendon xanthomas in a patient with normal plasma cholesterol levels

**FIGURE 3. Achilles tendon xanthomas in a patient with cerebrotendinous xanthomatosis.<sup>9</sup>**



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and a normal lipoprotein profile should trigger an investigation of CTX as a potential underlying cause.<sup>10</sup> In addition, xanthomas related to CTX have even been reported in the lung, bones, and central nervous system.<sup>1</sup>

### **Neurologic Clinical Manifestations**

Neurologic signs and symptoms of CTX usually appear after the second decade, but psychiatric manifestations such as behavioral/personality disorders or learning disabilities may appear earlier in the disease.<sup>4,11</sup> As with diarrhea, neurologic symptoms are not highly specific for CTX. However, progressive neurologic symptoms in a patient with juvenile cataract or a history of juvenile cataract are an important indication for a CTX workup.<sup>11,12</sup>

Intellectual impairment is present in some patients with CTX beginning in infancy; however, most have normal or only mildly impaired intellectual function until they reach puberty. More than half of affected patients develop dementia, with slow deterioration in cognitive function starting in their 20s. Approximately 50% of individuals with CTX also report seizures. Neurologic symptoms typically do not develop until adulthood, although in some cases they have an earlier onset. Pyramidal signs (eg, paresis, bulbar palsy) and/or cerebellar signs usually manifest between the ages of 20 and 30 years. Peripheral neuropathy is typically evident on electrophysiological studies, and it manifests clinically as distal muscle atrophy and pes cavus. Other neurologic manifestations of CTX can include spasticity and ataxia.<sup>5,6</sup> A spinal form of CTX has been reported in which spastic paraparesis and myelopathy are the main clinical symptoms, and intellect is almost always normal.<sup>1,3</sup>

Neuropsychiatric symptoms may be prominent, such as behavioral changes, hallucinations, agitation, aggression, depression, and suicide attempts.<sup>1,4</sup>

To study the disorder's psychiatric manifestations, Fraidakis reviewed all MEDLINE reports on CTX that were published

in English, Dutch, French, German, Italian, Japanese, or Spanish between 1937 and 2012.<sup>4</sup> A total of 425 patients were identified, and psychiatric manifestations were reported for 54 of them (12.7%).<sup>4</sup> However, only 2.5% of the 54 patients presented with fundamentally psychiatric symptoms early in the disease course, without overt neurologic disease. The earlier the onset of psychiatric symptoms, the milder their severity, with personality/behavioral disorder, irritability, and aggression being the most prominent psychiatric symptoms in patients younger than age 25 years. The researcher cautioned clinicians against disregarding irritability, aggression, attention-deficit hyperactivity disorder, and oppositional-defiant disorder in children and adolescents, as these conditions may be misdiagnosed. He suggested that such symptoms, along with the signs and symptoms of CTX (eg, diarrhea and cataracts) should prompt a thorough neurologic evaluation with a complete physical and ophthalmologic checkup, especially if the parents are consanguineous, which increases the probability of disorders that have an autosomal recessive inheritance pattern.<sup>4</sup>

### Other Clinical Manifestations

Additional signs of CTX have been reported occasionally, mostly in older patients:<sup>1,6</sup>

#### In and around the eye

- Optic nerve atrophy
- Myelinated ocular nerve fibers
- Optic disc paleness
- Premature retinal senescence with retinal vessel sclerosis
- Cholesterol-like deposits along ocular vascular arcades
- Palpebral xanthelasmas
- Proptosis

#### Additional systemic manifestations

- Premature atherosclerosis
- Coronary artery disease
- Gallstones
- Granulomatous lesions in the lumbar vertebrae and femur
- Thoracic kyphosis
- Hypothyroidism
- Extrapyramidal signs, including dystonia and atypical parkinsonism
- Premature osteopenia or osteoporosis with bone fracture and loss of teeth

► **LEARNING POINT:** Common presenting signs and symptoms of CTX are infantile-onset chronic diarrhea; juvenile bilateral cataracts; tendon xanthomas; neurologic disorders such as low intelligence, spasticity, ataxia, epilepsy, and peripheral neuropathy; and psychiatric/behavioral problems. The presence of juvenile-onset bilateral cataracts is almost always a universal sign among patients with CTX, occurring in up to 85% of cases with or without the other hallmark symptoms.<sup>1,7</sup>

### Laboratory Findings

Typical laboratory findings in patients with CTX are elevated levels of plasma cholestanol and bile alcohols, along with increased urinary excretion of bile alcohol glucuronides. In contrast, plasma cholesterol levels and the lipoprotein profile are typically within or below the normal ranges.<sup>11</sup> Molecular analysis of the *CYP27A1* gene provides a definitive diagnosis.<sup>6</sup>

## DIAGNOSTIC TOOL

There is typically a substantial delay from the onset of CTX symptoms to diagnosis. An Italian research team recently reviewed 170 cases reported between 1982 and 2013 in Europe (Italy, Netherlands, Spain, Belgium, Germany, United Kingdom), North America (United States), Africa (Tunisia), and Asia (Israel, China).<sup>6</sup> Patients typically presented with their first symptoms during childhood or adolescence (age 9 to 19 years), and cataract was usually diagnosed by the second decade. Still, on average, the diagnosis of CTX was not made until the fourth decade (age 34 to 38 years), an average delay in diagnosis of 20 to 25 years.<sup>6</sup>

To address this problem, the team developed a “suspicion index” (**Table 1**).<sup>6</sup> It is based on weighted scores for common clinical indicators that the researchers derived from their analysis of the 170 worldwide cases. When assessing a patient, they assign 100 points to each very strong indicator, 50 points to each strong indicator, and 25 points to each moderate indicator, as shown in Table 1. (The researchers explain that they consider tendon xanthomas a stronger indicator than cataract because it is more specific for CTX.) They recommend that patients with a total score  $\geq 100$  should have assessment of serum cholestanol concentrations, which should be measured in the absence of treatment with bile acids, statins, and corticosteroids. Patients with abnormally high plasma cholestanol concentrations should proceed to *CYP27A1* gene sequencing.

**TABLE 1. Suspicion Index for Diagnosing CTX<sup>6</sup>**

Indicators	Family History	Systemic	Neurological
A) Very strong (score = 100)	A1) Sibling with CTX	A2) Tendon xanthomas	
B) Strong (score = 50)	B1) Consanguineous parents	B2) Juvenile cataract	B5) Ataxia (a) and/or spastic paraparesis (b)
		B3) Childhood-onset chronic diarrhea	B6) Dentate nuclei signal alterations at MRI
		B4) Prolonged unexplained neonatal jaundice or cholestasis	B7) Intellectual disability (a) and/or psychiatric disturbances (b)
C) Moderate (score = 25)		C1) Early osteoporosis	C2) Epilepsy
			C3) Parkinsonism
			C4) Polyneuropathy

CTX, cerebrotendinous xanthomatosis; MRI, magnetic resonance imaging. Reprinted with permission<sup>6</sup>

The researchers consider 2 conditions sufficiently suggestive of CTX to warrant *CYP27A1* sequencing without previous cholestanol assessment: a total score  $\geq 200$  with at least 1 very strong or 4 strong indicators, or a sibling with genetically confirmed CTX.

This suspicion index was retrospectively applied to 55 of their own patients with CTX (members of 39 unrelated families) who had been evaluated by 1 of 3 neurologists experienced in CTX.<sup>6</sup> They found that use of the index would have substantially lowered the age at which the patients received a diagnosis: the mean age at diagnosis had been  $35.5 \pm 11.8$  years, but with the index, a score of  $\geq 100$  would have been reached at a mean age of  $10.6 \pm 9.8$  years and a score of  $\geq 200$  would have been reached at a mean age of 24.1 years.<sup>6</sup>

►► **LEARNING POINT:** Pediatric ophthalmologists should inquire about infantile-onset diarrhea, tendon xanthomas, and neurologic signs in all children and young adults presenting with unexplained bilateral cataract or lenticular deposits. This is particularly true if the cataracts are composed of fleck opacities with anterior or posterior capsular opacity. In children with signs or symptoms suggestive of CTX, especially unexplained bilateral cataracts, a diagnostic workup should be performed, and a “suspicion index” is available to assist with this. The index has been developed to help clinicians diagnose CTX and to guide further testing, but it is not confirmatory in itself. The gold standard for diagnosis is molecular analysis of the *CYP27A1* gene.

## DIFFERENTIAL DIAGNOSIS

Familial hypercholesterolemia, sitosterolemia, and Smith-Lemli-Opitz syndrome (SLOS) can have some clinical similarities to CTX (**Table 2**).<sup>11,13</sup> Familial hypercholesterolemia and other forms of autosomal dominant hypercholesterolemias are potential causes of tendon xanthomas. However, in patients

with familial hypercholesterolemia, laboratory testing typically shows increased levels of total cholesterol and low-density lipoprotein cholesterol, which are not features of CTX. In addition, studies of cardiac function may be abnormal.<sup>10,13</sup>

Tendon xanthomas can also be caused by sitosterolemia. This disorder, mutations in the *ABCG5* and *ABCG8* genes, results in increased absorption and decreased excretion of plant sterols. Its clinical features are premature atherosclerosis, thrombocytopenic purpura, and extensive tuberous xanthomas as well as tendon xanthomas.<sup>11</sup>

SLOS has many signs and symptoms that are also found in CTX, including juvenile cataract and xanthomas. SLOS is an autosomal recessive disorder associated with mutations in the *DHCR7* gene that reduce or eliminate the activity of 7-dehydrocholesterol reductase, the enzyme responsible for the final step in cholesterol production.<sup>14</sup> In mild cases, the patient may have only minor physical abnormalities but have learning and behavioral dysfunction. However, people afflicted with SLOS usually present with microcephaly, hypotonia, and hearing and speech problems. Premature cataracts are also common. Unlike patients with CTX, those with SLOS have hypocholesterolemia.<sup>13</sup>

There is some overlap in biochemical findings for CTX and SLOS. All patients with SLOS have increased levels of 7-dehydrocholesterol in both plasma and tissues,<sup>15</sup> and this observation has also been made for some patients with CTX.<sup>13</sup> The primary laboratory findings that differentiate CTX from other disorders that present with xanthomas are the high plasma and tissue levels of cholestanol and the normal to low concentration of plasma cholesterol in patients with CTX. In addition, in CTX there is decreased formation of chenodeoxycholic acid as a result of impaired primary bile acid synthesis, and elevated levels of bile alcohols and their glycoconjugates in bile, urine, and plasma.<sup>1</sup>

## CASE PRESENTATION: March 18, 2004

The geneticist obtained additional information from Betty's pediatric gastroenterologists. Previous bowel workups had included culture, ova and parasite examinations, and testing for *Clostridium difficile* toxin, fecal fat, pancreatic elastase, sweat chloride, and antigliadin antibodies (all negative). Betty had experienced only minimal improvement in stool frequency as a result of her treatment with loperamide.

The geneticist also gathered additional information about Betty's family ancestry. Her father is German, with maternal ancestry that includes Norwegian, German, Czech, and French. Betty has a younger sibling who is unaffected (a brother, age 7 at time of presentation).

A physical examination at the time of the genetics evaluation revealed that Betty's weight was in the 25th to 50th percentile, and her height was in the 75th percentile. She was nondysmorphic in appearance. Of note, there were no xanthomas on examination. However, the findings thus far raised the suspicion of CTX. Plasma and urine were drawn. The workup was to include mucopolysaccharide and oligosaccharide screens, plasma amino acids, urine organic acids, urine amino acids, urine electrolytes, and profiles of lactate, carnitine, and acyl carnitine. An order for TORCH titers (toxoplasmosis, other viruses, rubella, cytomegalovirus, and herpes simplex virus) was added later, prior to cataract surgery.

The geneticist indicated that Betty could proceed to cataract surgery despite the pending test results and possible need for metabolic treatment.

**TABLE 2. Comparison of CTX With Disorders That Have Similar Signs and Symptoms<sup>11,13</sup>**

Disorder	Key Clinical Features	Underlying Defect	Clue(s) to Differential Diagnosis
<b>CTX</b>	Juvenile bilateral cataracts, chronic diarrhea during childhood, tendon xanthomas, neurologic and psychiatric problems	Mutation in the <i>CYP27A1</i> gene results in sterol 27-hydroxylase deficiency, leading to accumulation of cholestanol	Normal lipid profile, increased plasma cholestanol levels, increased bile alcohols in plasma and/or urine
<b>Familial hypercholesterolemia</b>	Coronary heart disease, tendon and tuberous xanthomas	Problems with LDL receptors result in accumulation of lipoproteins in the tissues	No diarrhea or neurologic symptoms; elevated plasma level of LDL cholesterol
<b>Sitosterolemia</b>	Tendon and tuberous xanthomas, accelerated atherosclerosis, thrombocytopenic purpura, spastic paraparesis may occur	Mutations in the <i>ABCG5</i> and <i>ABCG8</i> genes result in increased absorption of plant sterols	No diarrhea or neurologic symptoms; very high plasma levels of phytosterol and normal or slightly elevated plasma cholesterol level
<b>Smith-Lemli-Opitz syndrome</b>	Juvenile cataract, xanthomas, learning disorders and behavioral problems, microcephaly, hypotonia, hearing and speech problems	Mutations in the <i>DHCR7</i> gene reduce or eliminate the activity of 7-dehydrocholesterol reductase, the enzyme responsible for the final step in cholesterol production	Hypocholesterolemia

CTX, cerebrotendinous xanthomatosis; LDL, low-density lipoprotein.

Definitive diagnosis of CTX is achieved through molecular analysis of the *CYP27A1* gene,<sup>6</sup> the only gene in which mutations are known to cause CTX.<sup>1</sup> Because CTX is inherited in an autosomal recessive fashion, a sibling of a person with CTX has a 25% possibility of having symptomatic CTX, a 50% possibility of being an asymptomatic CTX carrier, and a 25% chance of not having CTX and not being a carrier.<sup>1</sup>

►► **LEARNING POINT:** To distinguish CTX from disorders that have similar signs and symptoms, it is useful to know that CTX is the only one that presents with a normal lipid profile.

## DISCUSSION: IMAGING

MRI studies of the brain are an important component of the diagnostic workup for CTX. The major neuroradiologic hallmark of CTX is bilateral MRI signal abnormalities of the cerebellar dentate nuclei.<sup>6</sup> Many patients also have diffuse cerebral and cerebellar atrophy and bilateral focal cerebellar lesions.<sup>3,6,11,16</sup> However, not all patients with CTX have abnormalities on MRI.

►► **LEARNING POINT:** A normal MRI does not rule out CTX.

### CASE PRESENTATION:

**June 17, 2004**

The geneticist reviewed the results of the tests ordered at the previous visit. Betty's plasma cholesterol was 147 mg/dL, which was normal (optimal, <200 mg/dL), but plasma cholestanol was elevated at 3.7 mg/dL (normal, <0.2 mg/dL). In addition, Betty had elevated levels of plasma bile alcohols (5.63 µg/mL) and urine alcohols (30.1 µg/mL).

Betty's genetic profile suggested that she is homozygous for CTX. These findings were considered diagnostic for CTX. Genetic testing showed that Betty's brother does not have CTX.

Owing to Betty's putative learning disorder and potentially other neurologic complications of CTX, the geneticist recommended magnetic resonance imaging (MRI) and a neurology consultation.

In August 2004, a 24-hour electroencephalogram was abnormal but not consistent with epilepsy. Betty's MRI was normal. The neurologist recommended neuropsychiatric evaluation.

### CASE PRESENTATION:

**October 6 and 13, 2004**

The neuropsychiatrist evaluated the results of the Wechsler Intelligence Scale for Children-III testing done at Betty's school 1 year prior to her presentation to the ophthalmologist. At that time she had a verbal IQ of 85 (bottom of average range) and a performance IQ of 69 (far below the normal range). However, these scores had not qualified her for special education services.

The neuropsychiatric evaluation revealed that Betty had weaknesses in visual memory, slowed processing speed and executive functioning, and deficits in basic number skills, numeric reasoning, and mathematic operations.

**Table 3** summarizes the follow-up of Betty's case from initial presentation through 2012.

**TABLE 3. Summary of Case Presentation: “Betty,” a 10-Year-Old Girl With CTX**

Date	Event/Finding
3/3/2004	<ul style="list-style-type: none"> <li>Initial presentation to ophthalmologist<sup>a</sup></li> </ul>
3/18/2004	<ul style="list-style-type: none"> <li>Genetics evaluation<sup>a</sup></li> </ul>
4/16/2004	<ul style="list-style-type: none"> <li>Ophthalmology follow-up visit</li> <li>Vision decreased to 20/100 in each eye; exophoria stable</li> <li>Cataract surgery was scheduled</li> </ul>
6/2/2004	<ul style="list-style-type: none"> <li>Cataract surgery was performed on the right eye, including placement of a SA60AT 23.5 diopter lens in the capsular bag, without posterior capsulectomy</li> </ul>
6/17/2004	<ul style="list-style-type: none"> <li>Genetics follow-up visit<sup>a</sup></li> </ul>
6/18/2004	<ul style="list-style-type: none"> <li>Ophthalmology follow-up visit</li> <li>Vision 20/30–2 uncorrected in right eye; 20/80 in unoperated left eye</li> </ul>
7/7/2004	<ul style="list-style-type: none"> <li>Cataract surgery on left eye</li> <li>Placement of SA60AT 23.5 diopter lens in the capsular bag, without posterior capsulectomy</li> </ul>
7/19/2004	<ul style="list-style-type: none"> <li>Ophthalmology follow-up visit</li> <li>Visual acuity 20/30+2 right eye; 20/40–1 left eye; 20/20 each eye with refraction</li> </ul>
8/2004	<ul style="list-style-type: none"> <li>Neurology evaluation</li> <li>Abnormal 24-hour EEG, but not consistent with epilepsy</li> <li>MRI normal</li> <li>Neuropsychiatric evaluation recommended</li> </ul>
10/6/2004 & 10/13/2004	<ul style="list-style-type: none"> <li>Neuropsychiatric evaluations<sup>a</sup></li> </ul>
11/8/2004	<ul style="list-style-type: none"> <li>Genetics follow-up visit; patient was doing well, with improved symptoms on treatment</li> </ul>
11/11/2004	<ul style="list-style-type: none"> <li>Ophthalmology follow-up visit</li> <li>To confirm that neuropsychiatric findings were not related to vision, a 24-2 Humphrey visual field was performed and was normal</li> </ul>
2005–2009	<ul style="list-style-type: none"> <li>YAG capsulotomies were performed on 10/26/05 in the right eye and 6/15/06 in the left eye. Of note, the posterior capsule on the left contracted and required repeat YAG capsulotomy twice, on 5/29/08 and 8/13/09</li> </ul>
12/7/2012	<ul style="list-style-type: none"> <li>Last visit to pediatric ophthalmologist, 8.5 years after cataract surgery</li> <li>Vision was 20/20 in each eye with correction; manifest refraction OD –1.25 +2.00 x 096, OS –1.00 +1.50 x 085 had been stable for 7 years</li> <li>Strabismus had resolved after surgery, and stereopsis had improved to 60 arc seconds, likely related solely to improved acuity</li> </ul>

CTX, cerebrotendinous xanthomatosis; EEG, electroencephalogram; MRI, magnetic resonance imaging; OD, oculus dexter; OS, oculus sinister; YAG, yttrium aluminum garnet.

<sup>a</sup>Details in text.

## CONCLUSIONS

Pediatric ophthalmologists can play a pivotal role in the early diagnosis of CTX, a rare lipid storage disease that can have serious consequences, including dementia, cerebellar ataxia, and spinal cord paresis, if not treated early. Common systemic manifestations of CTX include bilateral juvenile-onset cataracts, infantile-onset chronic diarrhea, tendon xanthomas, psychiatric disturbances, and neurologic conditions. Whenever a child or adolescent presents with unexplained bilateral cataracts, a workup should be designed to detect or rule out CTX, with special attention to whether the child has developmental delay, a history of chronic diarrhea, a sibling with CTX, or parents who are blood relatives. A normal MRI does not rule out CTX. A suspicion index has been developed to assist clinicians with making a diagnosis of CTX and to guide further testing, but it is not confirmatory in itself. The gold standard for diagnosis is molecular analysis of the *CYP27A1* gene. Suspicion of CTX should warrant a plasma cholestanol level and/or a referral to a metabolic specialist. This is critical to prevent irreversible neurologic damage. Currently, most affected individuals are diagnosed late or not at all, but this can be improved with awareness on the part of pediatric ophthalmologists.



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