KEY SIGNS INDICATING THAT YOUR PATIENT WITH IDIOPATHIC BILATERAL CATARACTS MAY HAVE A TREATABLE CONDITION

Help Improve Outcomes in Cerebrotendinous Xanthomatosis (CTX) With Earlier Diagnosis

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Untreated or undiagnosed CTX may lead to serious short- and long-term clinical implications.[1,2]

What is CTX?

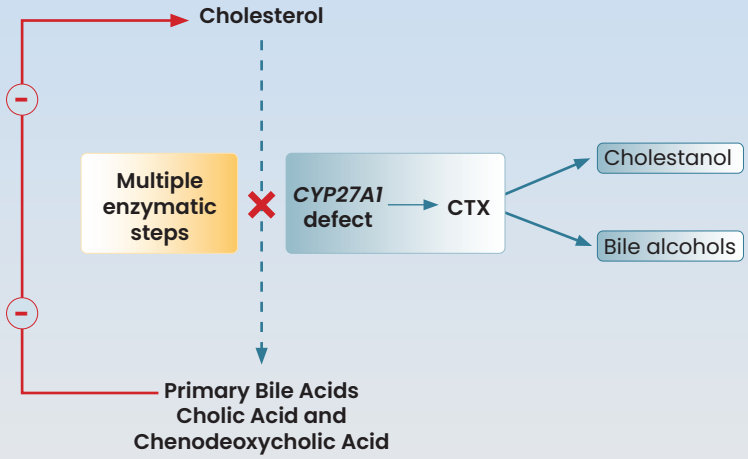
CTX is a rare autosomal-recessive lipid storage and metabolic disease.[1,3,4]

MECHANISM OF DISEASE

- CTX is caused by mutations in the *CYP27A1* gene, which codes for the mitochondrial enzyme of sterol-27-hydroxylase that converts cholesterol to bile acids.[1]

- Sterol-27-hydroxylase deficiency reduces the production of cholic acid and chenodeoxycholic acid (CDCA)—the most common endogenous bile acids.[5-7]
- As bile acids are inhibitors of CYP7A1, a negative feedback mechanism is lost and the process of cholesterol elimination is interrupted.[6,8]
- The negative feedback mechanism leads to toxic effects due to[6,8]:
  - Increased levels of bile alcohols and other bile acid precursors, including 7-hydroxycholesterol and 7α, 12α-dihydroxy-4-cholesten-one.
  - Accumulation of cholestanol throughout the body.

The Mechanism of CTX: Interruption Due to *CYP27A1* Defect[8]



IMPACT OF DISEASE

Untreated CTX May Progress to Irreversible Neurologic Problems.[1,9,10]

Without early diagnosis and management, neurologic problems can progress, leading to physically disabling neurological dysfunction, psychiatric disturbances, intellectual disability, and even dementia.[1,2]

Challenge of Diagnosis

- CTX is challenging to diagnose owing to its variability and multisystemic effects.[1]

DELAY IN DIAGNOSIS

- Current mean age (±SD) at diagnosis is 35.5 ± 11.8 years.[1]
- CTX signs and symptoms are variable in onset and severity and not every patient experiences all clinical manifestations.[1]

> *Because the clinical manifestations of CTX affect different organ systems, patients are likely to present to different specialists, potentially leading to delayed diagnosis and underdiagnosis.*[1,11]

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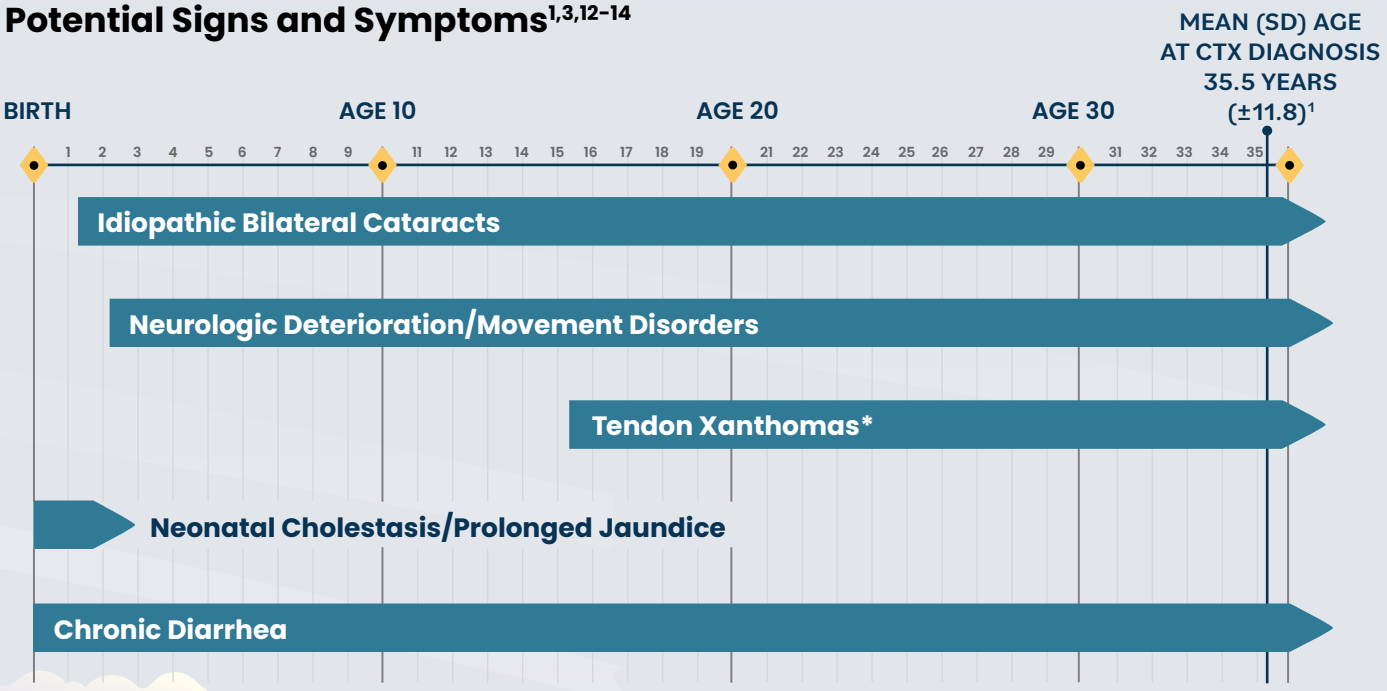
KEY CTX SIGNS AND SYMPTOMS

CTX causes an array of clinical manifestations.[1]

If your patient has more than one of the below signs and symptoms, you should suspect CTX.[1,3,12-14]

Potential Signs and Symptoms[1,3,12-14]



*A small number of genetic disorders affect lipoproteins and can lead to xanthomas: cerebrotendinous xanthomatosis (CTX), familial hypercholesterolemia, and sitosterolemia.[11]

Deep Dive on Idiopathic Bilateral Cataracts

Idiopathic early-onset bilateral cataracts represent a key opportunity to diagnose CTX.[10]

- **Idiopathic bilateral cataracts affect ~85% of patients with CTX.[9,12,*]**
- Cataracts often present between the ages of 4 and 18 years.[12,†]
- Patients with juvenile-onset bilateral cataracts had up to a **500-fold** higher CTX prevalence than in the general population.[10]
- **~2 of every 100** patients with early-onset bilateral cataracts were diagnosed with CTX.[10]
- Among patients with a known neurologic disorder presenting with early-onset cataracts, CTX may be the second most common cause after myotonic dystrophy.[15]

In CTX, cataracts are caused by a buildup of cholestanol in the lens.[16]

- CTX cataracts may be somewhat distinctive in their appearance or morphology.[16]
  - The nature of the crystalline lens opacities has been described as zonular, anterior, or posterior opacities that were like spokes, dots, flecks, or snowflakes, or a combination of the above.[16]

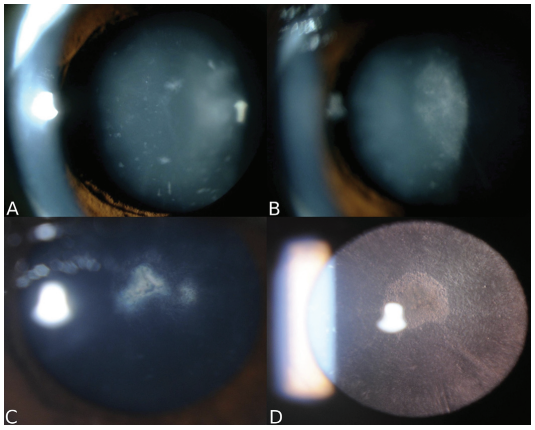


Figure 2. A, B, Fleck opacities and posterior capsular cataract opacity can be appreciated in the right eye of patient 2.2. The left eye was similar (not shown). **C, D,** Fleck opacities and anterior lens opacity can be appreciated in the right eye of patient 2.3. Without retroillumination (**C**), fleck opacities are barely discernible inferonasally, whereas with retroillumination (**D**), multiple flecks are appreciated as well as cortical changes. There was also mild posterior capsular lens opacity (not visualized). The left eye was similar (not shown).

*Other causes of bilateral cataracts in children include: galactosemia,[17] diabetes,[18] uveitis associated with chronic juvenile arthritis,[19] history of chronic corticosteroid use[20] or whole body irradiation,[21] hypoglycemia,[22,23] or hypocalcemia.[24,25]

†In CTX, cataracts usually develop in the first 3 decades of life, although a smaller number of patients develop cataracts later in life, after neurologic symptoms are already advanced.[12,26]

SCOUT BY MIRUM: Early-Onset Bilateral Cataracts Genetic Panel*

Mirum Pharmaceuticals has partnered with PreventionGenetics, a College of American Pathologists-accredited laboratory,† to offer a no-cost patient genetic test to identify up to 66 causes[27] of early-onset bilateral cataracts.

Genes included on the Early-Onset Bilateral Cataracts Genetic Panel[27]							
ABHD12	*ADAMTSL4*	*ALDH18A1*	*BCOR*	*BEST1*	*BFSP1*	*BFSP2*	*CHMP4B*
COL11A1	*COL18A1*	*COL2A1*	*COL4A1*	*CRYAA*	*CRYAB*	*CRYBA1*	*CRYBA2*
CRYBA4	*CRYBB1*	*CRYBB2*	*CRYGC*	*CRYGD*	*CRYGS*	*CYP27A1*	*DYNC1H1*
EPHA2	*ERCC2*	*FAM126A*	*FOXE3*	*FTL*	*FYCO1*	*FZD4*	*GALE*
GALK1	*GALT*	*GCNT2*	*GJA3*	*GJA8*	*GLA*	*HSF4*	*LEMD2*
LIM2	*LONP1*	*MAF*	*MIP*	*MIR184*	*MYH9*	*NACC1*	*NDP*
NF2	*NHS*	*OPA3*	*PAX6*	*PITX3*	*P3H2*	*RAB3GAP1*	*RDH11*
RECQL4	*SC5D*	*SIL1*	*SLC16A12*	*TFAP2A*	*TGM3*	*UNC45B*	*VIM*
WRN	*XYLT2*						

Criteria for No-Cost Testing*

Any questions can be addressed by the PreventionGenetics genetic counselors and staff at **(715) 387-0484**.

Click **here** to request that a Mirum representative contact you.

***Program may be canceled or changed at any time.**

†Note that Mirum Pharmaceuticals cites the above-named external testing resource for information purposes only, and does not endorse or guarantee in any way the services or advice provided by them.

‡Not known to be due to infectious causes, trauma, etc.

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27. PreventionGenetics Panel Data.

CASE STUDY:
9-year-old child with bilateral cataracts

Patient referred to an ophthalmologist

Presenting symptoms

- Decreased vision over several months

Medical history

- Significant for diarrhea and nonverbal learning disorder

Examination

- Uncorrected distance visual acuity: 20/80 OU
- Uncorrected near acuity: 20/50 OU
- Manifest refraction: 0.75+0.50 X 90 OU, with a corrected distance acuity of 20/60 OD and 20/80 OS
- Complete dilated examination: remarkable for the presence of a cataract in each eye, described as a diffuse nuclear haze on slit lamp examination, with mild posterior capsular opacification
- Metabolic workup: plasma 5-cholestanol level was markedly elevated at 3.7 mg/dL (normal <0.2 mg/dL), which was **suggestive of CTX**

Outcome

- Sequential bilateral cataract surgery with intraocular lens placement corrected visual acuity to 20/20 OU
- After 6 years, due to early diagnosis and appropriate management, no further clinical manifestations of CTX had developed

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CTX
Management Ahead

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