KEY SIGNS INDICATING THAT YOUR PATIENT WITH MOVEMENT DISORDERS, INCLUDING ATAXIA, 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]

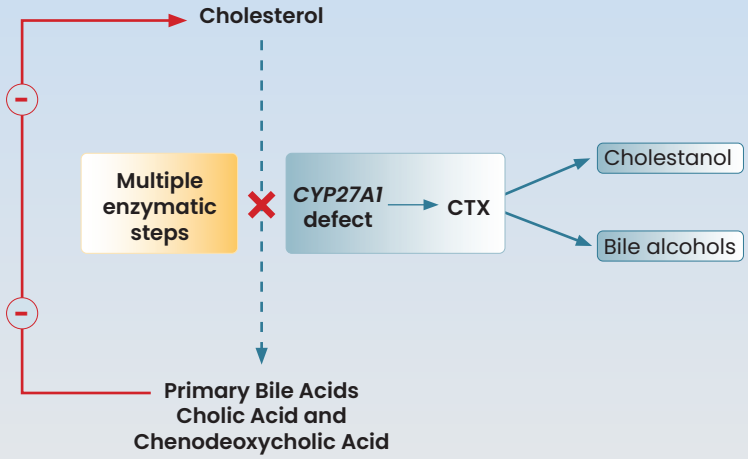
What is CTX?

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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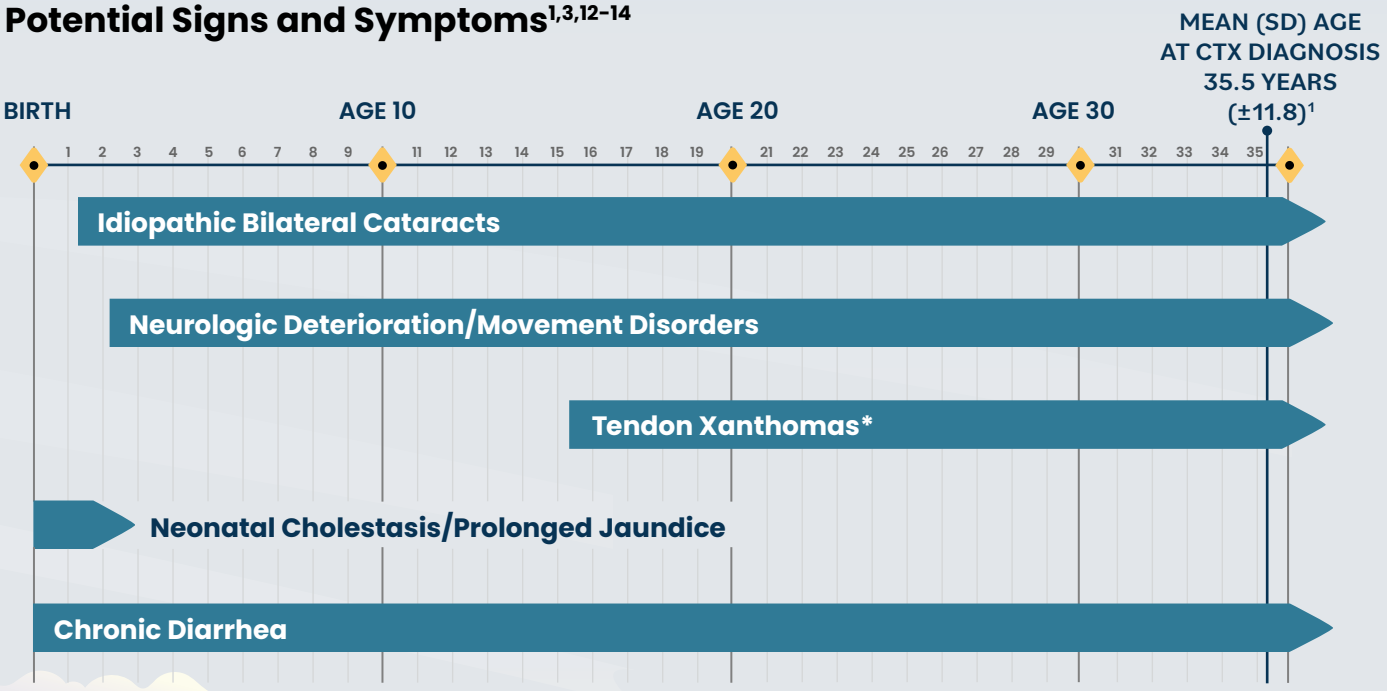
KEY CTX SIGNS AND SYMPTOMS

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.

Deep Dive on Neurologic Deterioration/Movement Disorders

- **CTX can lead to serious neurologic problems.**[1,9,10]
- **Ataxia is one of the key manifestations of progressive neurological dysfunction in patients with CTX.**[1,15]
- Consider testing for CTX if your patient has a history of:

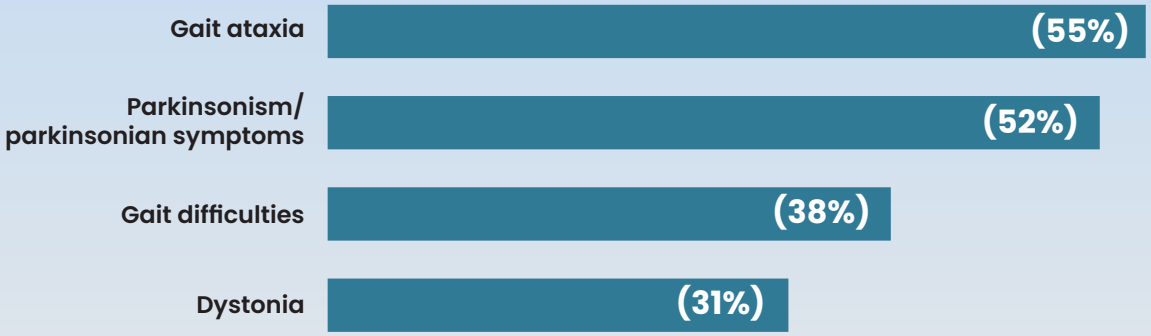
Idiopathic Bilateral Cataracts

- **Affects ~85% of patients with CTX**[9,12]

+

Neurologic Deterioration/Movement Disorders

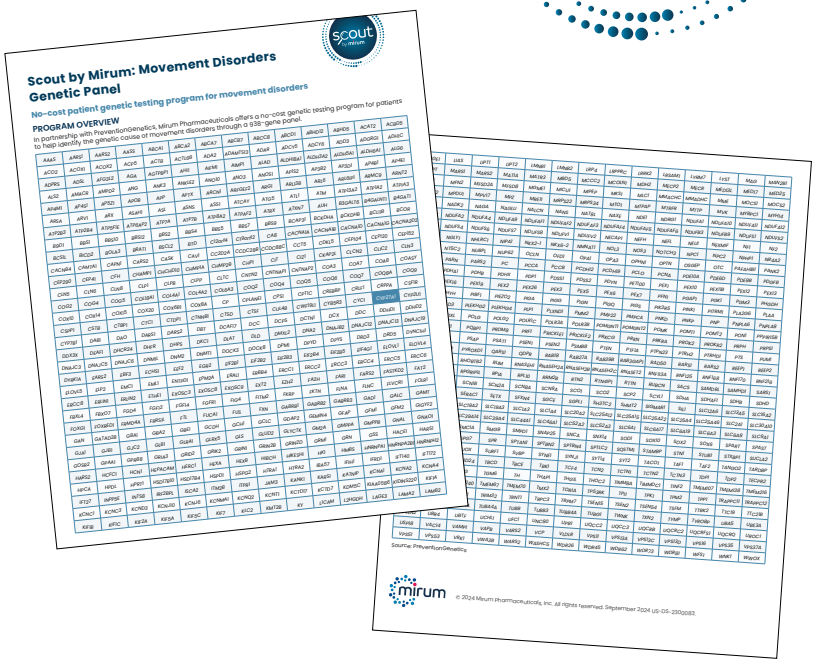
- **Patients with CTX frequently present with movement disorders (frequency)**[16,17]



Patients with CTX whose diagnosis is missed or delayed may face severe intellectual and physical disability in their early adult years.[1,12]

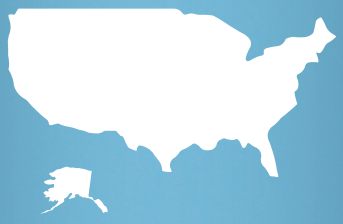
- Patients with advanced CTX show evidence of lipid deposits and loss of white matter in many areas of the brain.[18,19]
- Early developmental milestones may be achieved punctually, but patients then begin to fall behind.[1]
  - Patients may exhibit poor school performance, learning difficulties, sustained infantile behavior, and lack of age-appropriate self-care skills.
- ~50% have experienced seizures.[9]
- ~70% have pyramidal signs, such as increased deep tendon reflexes, pathologic reflexes, and spastic paraplegia.[1,12,20,21]
- 60% have cerebellar signs.[12]
  - Neurological imaging has revealed progressive unsteady paraparetic gait as a predominant symptom of CTX in adults.[22]
  - Cerebellar ataxia usually becomes evident, presenting in the second or third decade of life.[1,23]

SCOUT BY MIRUM: Movement Disorders Genetic Panel*



Mirum Pharmaceuticals has partnered with PreventionGenetics, a College of American Pathologists-accredited laboratory,† to offer a no-cost genetic test panel to identify up to 938 genes to help diagnose genetic causes of movement disorders.

Criteria for No-Cost Testing*



Patient resides in North America (US or Canada)

AND

Children and adults with clinically abnormal movements including, but not limited to, ataxia, dystonia, tremor, and parkinsonism

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.

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CASE STUDY:
A 55-year-old with tendon xanthomas

Presenting symptoms

- Admitted to the hospital for investigations relating to a slowly progressive paraparesia and joint deformities

Medical and family history

- Difficulty standing and walking since infancy
- Bilateral juvenile cataracts
- Unable to complete education because of intellectual disability
- 3 siblings died in childhood, one from an undiagnosed neurological disorder
- Unknown whether patient's parents were related

Physical and neurological examination

- Physical examination:
  - Tendon xanthomas—firm, round, noninflammatory, subcutaneous tumors measuring 6 cm in diameter over the knees and elbows, which adhered to tendons
  - Yellowish papules of 2 to 3 mm in diameter in the superior eyelid, compatible with xanthelasmas
- Neurological findings included:
  - Mental retardation, spastic-ataxic gait, bilateral Babinski sign, symmetric amyotrophia on inferior and superior extremities, and hyperactive deep tendon reflexes with associated left Achilles clonus
- Ligamentous hyperlaxity was observed
- Electroencephalogram showed a mild disorganization of the basic activity of theta waves

Laboratory testing and imaging studies

- Standard laboratory test values were normal
- Biopsy from the left knee:
  - Infiltrate of foam cells surrounded by fibrous tracts
  - Inflammatory cells such as lymphocytes, histiocytes, and neutrophils were observed around the foam cells in some areas and a cholesterol cleft was found
- Magnetic resonance imaging:
  - Cerebral and cerebellar atrophy and hyperintense signals in the mesencephalic peduncles, protuberance, and cerebellar hemispheres

Diagnosis/outcome

- Because of these signs and symptoms, CTX was suspected and later confirmed by laboratory testing
- Appropriate management was initiated; however, due to the advanced state of the patient's disease, only slight improvement in spasticity was noted

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