Prevalence of Cerebrotendinous Xanthomatosis (CTX) Among Patients Diagnosed With Juvenile-Onset Idiopathic Bilateral Cataracts

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RESULTS

- 447 patients were screened at 43 sites; 442 were enrolled and 28 (6.3%) underwent genetic testing
- Patient demographics are shown in **Table 1**

Table 1. Patient demographics

Characteristics	Overall (N=442)
Age at study entry, years	
Mean (SD)	11.1 (6.8)
Median (range)	9.8 (0.1-52.6)
Sex, n (%)	
Male	236 (53.4)
Female	206 (46.6)
Race*, n (%)	
White	316 (71.5)
Black or African American	77 (17.4)
Asian	19 (4.3)
Native Hawaiian or Other Pacific Islander	10 (2.3)
American Indian or Alaska Native	1 (0.2)
Other	18 (4.1)
Missing	27 (6.1)
Ethnicity, n (%)	
Non-Hispanic or Latino	340 (76.9)
Hispanic or Latino	71 (16.1)
Not Applicable	31 (7.0)

*Race was self-reported by patient or guardian. Patients with multiple races were counted in each attributed race category.

- 274 patients experienced at least 1 CTX-related symptom other than cataracts (**Table 2**)
  - The most common were non-cataract eye disorders (29.4%), developmental delay (23.1%), and learning disability (21.3%)

Table 2. CTX medical history

Patients, n (%)	Overall (N=442)
Patients with at least one CTX clinical finding	**274 (62.0)**
Neurocognitive disorders	**147 (33.3)**
Learning disability	94 (21.3)
Neuropsychiatric symptoms	73 (16.5)
Behavior disorder	59 (13.3)
Autism spectrum disorder	32 (7.2)
Eye disorders*	**130 (29.4)**
General disorders	**124 (28.1)**
Developmental delay	102 (23.1)
Gait disturbance	64 (14.5)
Nervous system disorders	**121 (27.4)**
Dysarthria	71 (16.1)
Fine motor skill dysfunction	67 (15.2)
Seizure	43 (9.7)
Motor dysfunction	42 (9.5)
Cognitive disorder	26 (5.9)
Dystonia	21 (4.8)
Hyperreflexia	12 (2.7)
Tremor	11 (2.5)
Paresthesia	10 (2.3)
Gastrointestinal disorders	**61 (13.8)**
Dental disorder	36 (8.1)
Diarrhea	28 (6.3)
Hepatobiliary disorders	**59 (13.3)**
Jaundice	54 (12.2)
Liver disorder	8 (1.8)
Biliary tract disorder	5 (1.1)
Patient evaluation	**50 (11.3)**
Investigation abnormal	38 (8.6)
Electroencephalogram abnormal	29 (6.6)
Social circumstances	**46 (10.4)**
Loss of personal independence in daily activities	46 (10.4)
Musculoskeletal and connective tissue disorders	**20 (4.5)**
Foot deformity	20 (4.5)
Osteoporosis	1 (0.2)

*Because bilateral cataracts were required for study enrollment, this category refers to eye disorders other than bilateral cataracts.
CTX, cerebrotendinous xanthomatosis.

- 423 patients had available PC and 281 had available UBA samples; laboratory results are shown in **Table 3**

Table 3. Laboratory testing results

	Overall (N=442)
Patients with PC, n	423
Mean (SD), mg/dL	0.30 (0.32)
Median (range), mg/dL	0.26 (0.10-4.21)
Patients with plasma total cholesterol, n	10
Mean (SD), mg/dL	161.7 (90.2)
Median (range), mg/dL	190.0 (0.3-251.0)
Patients with UBA, n	281
Negative, n (%)	277 (98.6)
Positive, n (%)	4 (1.4)
Patients with *CYP27A1* genetic testing*, n	28[†]
Negative, n (%)	24 (85.7)
Positive, n (%)	4 (14.3)

*Genetic tests were performed on patients with PC ≥0.4 mg/dL or positive UBA result. The percentage is calculated using the number of patients with non-missing result (ie, n) as the denominator.
[†]Two patients underwent genetic testing despite not meeting criteria. Both were negative.
PC, plasma cholestanol; SD, standard deviation; UBA, urine bile alcohol.

- CTX prevalence in patients with apparent idiopathic bilateral cataracts was 0.9% (95% CI: 0.3%-2.4%) (**Table 4**)
- In patients with apparent idiopathic bilateral cataracts with elevated PC or positive UBA, CTX prevalence was 15.4% (95% CI: 4.4%-34.9%)

Table 4. Laboratory testing results that prompted genetic testing

	Overall (N=442)
Patients with PC, n	423
Patients with PC ≥0.4 mg/dL, n (%, 95% CI*)	26 (6.1, 4.1-8.9)
Patients with UBA, n	281
Patients with a positive UBA result, n (%, 95% CI*)	4 (1.4, 0.4-3.6)
Patients with PC or UBA, n	428
Patients with a positive genetic test for CTX[†], n (%, 95% CI*)	4 (0.9, 0.3-2.4)
Patients with PC ≥0.4 mg/dL or positive UBA, n	26
Patients with a positive genetic test for CTX[†], n (%, 95% CI*)	4 (15.4, 4.4-34.9)

*Two-sided 95% confidence intervals were calculated using the exact Clopper-Pearson method.
[†]Genetic tests were performed on patients with PC ≥0.4 mg/dL or a positive UBA result.
CI, confidence interval; CTX, cerebrotendinous xanthomatosis; PC, plasma cholestanol; UBA, urine bile alcohol.

- Clinical characteristics and causative pathogenic variants of patients with CTX are shown in **Table 5**

Table 5. Clinical characteristics of patients with positive CTX genetic test

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Female	Male	Female
Age at enrollment, years	15	13	18	13
PC, mg/dL	3.17	3.22	4.21	3.33
UBA result	Positive	Positive	Positive	Positive
Clinical characteristics (age at onset, if known)	• Seizures (birth) • Developmental delay • Exotropia (8 y) • Frequent fractures (13 y) • Abnormal gait or balance • Cognitive decline • Learning disability • Foot deformity	• Liver disease (4 mo) • Biliary disease (4 mo) • Jaundice (4 mo) • Learning disability (7 y, 8 mo) • Seizures (10 y) • Abnormal EEG (10 y) • Cognitive decline (10 y) • Abnormal gait or balance (10 y) • Problems with fine motor control (10 y) • Frequent fractures (10 y)	• Unexplained chronic diarrhea (16 y) • Abnormal gait or balance (16 y) • Learning disability	• Jaundice (birth) • Learning disability (7 y)
***CYP27A1* gene variants**				
Allele 1	Known missense variant p.R127W:c.379C>T	Nonsense variant p.Q358X:c.1072C>T	Nonsense variant p.R231X:c.691C>T	Homozygous frameshift variant NM_000784.3: c.666_678delCGAGAAACGCATT
Allele 2	Novel frameshift variant c.1180_1181 delCT	Novel missense variant p.G472V:c.1415G>T	Synonymous variant p.Q85Q:c.255G>A	

EEG, electroencephalogram; mo, month; PC, plasma cholestanol; UBA, urine bile alcohol; y, year.

CONCLUSIONS

- CTX prevalence in patients with apparent idiopathic bilateral cataracts (0.9%, or 1:111) was higher than in total population estimates (1:44,000–3,400,000)[2]
- Participants in this study may not be representative of the entire population of patients with early-onset idiopathic bilateral cataracts
- Ophthalmologists can play an important role in diagnosing CTX earlier by conducting metabolic testing in young patients with bilateral cataracts
- Workup for patients with non-congenital early-onset idiopathic bilateral cataracts should include PC, UBA, and genetic testing in collaboration with a genetic counselor or geneticist, especially in those with elevated PC or UBA

DISCLOSURES

SFF: Investigator for Travere Therapeutics, Inc.; compensated for attendance to the CTX workshop; scientific advisor for Qlaris Bio, Inc.

BRN: Study investigator for Travere Therapeutics, Inc.; honoraria from Travere Therapeutics, Inc.

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INTRODUCTION

- CTX is a rare, autosomal recessive bile acid synthesis disorder that manifests diverse symptoms, including early-onset bilateral cataracts, early-onset chronic diarrhea, tendon xanthomas, and progressive neurological deterioration[1]
- CTX is often diagnosed and treated years after symptom onset, increasing the risk of progressive neurologic damage[1]
- Caused by biallelic pathologic variants in *CYP27A1*, a gene that codes for sterol 27-hyroxylase, CTX produces elevated plasma cholestanol (PC) and urinary bile alcohols (UBA)[1]
- Metabolic testing for CTX among children with idiopathic acquired bilateral cataracts may aid earlier diagnosis and treatment of CTX

OBJECTIVES

- To evaluate the prevalence of CTX in patients diagnosed with apparent idiopathic bilateral cataracts between the ages of 2 to 21 years
- The secondary objective was to assess other manifestations of CTX in these patients

METHODS

- This observational, multicenter study enrolled patients with early-onset apparently idiopathic bilateral cataracts in the United States
- Patients were excluded if they had a prior CTX diagnosis, had cataracts of known etiology, or were receiving cholic acid or chenodeoxycholic acid at screening
- Patients with PC levels ≥0.4 mg/dL or positive UBA prompted *CYP27A1* genetic testing at a Clinical Laboratory Improvement Amendment-certified laboratory

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