Cerebrotendinous Xanthomatosis

Possible Higher Prevalence Than Previously Recognized

Matthew T. Lorincz, MD, PhD; Shirley Rainier, PhD; Donald Thomas, BS; John K. Fink, MD

Background: Cerebrotendinous xanthomatosis (CTX) is a rare but treatable neurodegenerative disorder caused by 27-sterol hydroxylase (CYP27) deficiency.

Objective: To describe clinical features and results of genetic analysis in a family with CTX.

Design: Case report.

Setting: University hospital.

Subjects: A 54-year-old woman with CTX, her family members, and 115 white control subjects.

Main Outcome Measures: Results of clinical evaluation and magnetic resonance imaging of the brain in the affected subject; results of mutation analysis of the CYP27 coding sequence in the patient, her parents, and the control subjects.

Results: The proband and her affected sibling had classic features of CTX, including presenile cataracts, tendon xanthomas, diarrhea, and a complex neurodegenerative disorder. They were somewhat atypical, however, because their cataracts were congenital, cognitive impairment had been noted in childhood, and the white matter involvement was more severe than usual. The proband was shown to be homozygous for CYP27 mutation R362C. Similar analysis of 115 control subjects identified 1 subject who was a heterozygous carrier for this same CYP27 mutation.

Conclusions: The prevalence of CTX due to CYP27 mutation R362C alone is approximately 1 per 50,000 among white individuals. Although the disorder is rare, this incidence is substantially greater than previously recognized. Greater awareness of CTX is important because specific treatment is available.

Arch Neurol. 2005;62:1459-1463

Cerebrotendinous Xanthomatosis (CTX) is an autosomal recessive lipid storage disorder with variable clinical manifestations. Clinical signs of CTX include juvenile cataracts, tendon xanthomas, premature atherosclerosis, and progressive neurologic disturbance that includes dementia, pyramidal and extrapyramidal signs, ataxia, seizures, psychiatric disorders, and peripheral neuropathy. The disorder also may be associated with osteoarthritis, skeletal fracture, pes cavus, pulmonary insufficiency, endocrinopathy, renal and hepatic calculi, and childhood chronic diarrhea.¹⁻⁶

Cerebrotendinous xanthomatosis is due to homozygous mutation of the mitochondrial enzyme 27-sterol hydroxylase (CYP27),⁷ which is responsible for conversion of cholesterol to cholic and chenodeoxycholic acid. In CTX, reduced synthesis of cholic and chenodeoxycholic acid apparently results in failed feedback inhibition of cholesterol production, which in turn leads to the laboratory hallmarks of CTX: increased serum cholestanol concentration and elevated urinary bile alcohols. A recent study⁸ did not observe correlation between specific CYP27 mutations and particular CTX phenotypes.

In most ethnic groups, CTX is considered to be quite rare. Among Moroccan Jews, however, CTX is not rare and has an incidence of 1:108.⁹ Cerebrotendinous xanthomatosis is treatable. Oral supplementation with chenodiol has halted disease progression and led to significant neurologic recovery.¹⁰

We describe a family with CTX that had an unusual clinical presentation and disease course. We identified a greater-than-expected carrier frequency of the CYP27 mutation in control subjects, indicating that CTX has a substantially greater prevalence than currently recognized.

REPORT OF A CASE

HISTORY

A 54-year-old woman presented for evaluation of insidiously progressive tremor, in-
General physical examination of the proband showed visual impairment and 2 movable, nontender subcutaneous nodules, approximately 1 cm, over the right Achilles tendon. Neurologic examination disclosed disorientation to place and date, impaired short-term memory, and impaired ability to calculate and copy non-representational hand gestures. Palpomental sign was present. Speech was hypophonic with spastic and ataxic dysarthria. The patient had moderate generalized bradykinesia including facial bradykinesia with drooling. Pupils were irregular (previous cataract removal) although reactive to light. Results of funduscopys were normal. Extraocular movements were abnormal with marked saccadic intrusions into smooth-pursuit movements, square-wave jerks, hypermetric saccades, and nystagmus in all gaze directions. Upgaze was limited. Facial strength and sensation were normal. Hearing was intact. Tongue movements were slow. Muscle bulk and strength were normal throughout. Muscle tone was abnormal, with symmetric cogwheel rigidity in the upper extremities and symmetric lead pipe rigidity in the lower extremities. Finger tapping was slow bilaterally. Dysmetria was evident on finger-to-nose and heel-to-shin testing. Light touch and temperature sensations were preserved, but vibratory sense was diminished in the distal lower extremities. Symmetric hyperreflexia (3+) was noted at the biceps, triceps, brachioradialis, and quadriceps muscles. Ankle jerks were relatively diminished (1+ intensity). Jaw jerk was hyperactive (3+ intensity). Plantar responses were extensor bilaterally. The patient required assistance to arise from a chair and, with assistance, was able to take several small slow steps. Gait was wide based. Postural reflexes were diminished.

LABORATORY ANALYSIS

The plasma cholestanol level was elevated on 2 determinations (39.8 µg/mL and 43.2 µg/mL; normal adult value, ≤18 µg/mL). Levels of total serum cholesterol (222 mg/dL [5.7 mmol/L]), high-density lipoprotein cholesterol (69 mg/dL [1.8 mmol/L]), and low-density lipoprotein cholesterol (135 mg/dL [3.5 mmol/L]) were normal. Concentrations of leukocyte β-galactosidase and arylsulfatase, serum long-chain fatty acids, and results of copper analysis were normal.

NEUROIMAGING

Noncontrast magnetic resonance imaging of the brain demonstrated generalized, predominantly subcortical atrophy of the hemispheres, brain stem, and cerebellum. Deep white matter in the cerebral hemispheres and cerebellum demonstrated nearly confluent T2 signal intensity (Figure 2A-D). An abnormally increased T2 signal was also present in the substantia nigra, cerebral peduncles, and globus pallidus with involvement of the adjacent posterior limb of the internal capsule.

Noncontrast computed tomographic scans of the head (Figure 2E and F) of the proband's similarly affected sibling (subject V:2, Figure 1) obtained before his death
showed an attenuated signal in the subcortical white matter and cerebellar hemispheres and generalized cerebral atrophy with compensatory ventricular dilation.

MOLECULAR GENETIC ANALYSIS

This study was approved by the University of Michigan institutional review board. Control subjects for molecular genetic analysis were white volunteers of European ancestry who were older than 60 years and who had been examined and found not to have a personal or family history of neurologic disease. The DNA was extracted from peripheral blood leukocytes, and each CYP27 exon was amplified by polymerase chain reaction and sequenced as previously described.\textsuperscript{11,12} In the proband, the CYP27 coding sequence

Figure 2. Fluid-attenuated inversion recovery (FLAIR) and computed tomographic images of the proband and her sibling. A-D, FLAIR-weighted images of the proband (subject V:1, Figure 1) at 54 years of age at the level of the cerebellum (A), midbrain (B), basal ganglia and internal capsule (C), and cerebral cortex (D). The FLAIR images demonstrate pathological signal intensity in the deep cerebellum, cerebral peduncles, basal ganglia, and adjacent internal capsule, and periventricularly with a frontal predominance. The images also demonstrate global cortical atrophy with a frontal predominance. Computed tomographic images of the sibling (subject V:2, Figure 1) at the level of the cerebellum (E) and cerebral cortex (F) show an abnormal signal in the cerebellar hemispheres and periventricularly, as well as generalized atrophy.
finding a previously identified CYP27 gene mutation, neurodegenerative course. The diagnosis was confirmed by congenital cataracts, tendon xanthomas, and progressive signs of elevated plasma cholestanol level in the presence of Cerebrotendinous xanthomatosis was diagnosed on the basis of DNA sequencing. A heterozygous mutation was confirmed in this individual by DNA sequencing.

DIAGNOSIS AND TREATMENT

Cerebrotendinous xanthomatosis was diagnosed on the basis of elevated plasma cholestanol level in the presence of congenital cataracts, tendon xanthomas, and progressive neurodegenerative course. The diagnosis was confirmed by finding a previously identified CYP27 gene mutation, R362C. Treatment with chenodiol (250 mg 3 times daily) was initiated through collaboration with Gerald Salen, MD (University of Medicine and Dentistry, Newark, NJ).

Although our patient had many classic features of CTX (including cataracts, tendon xanthomas, diarrhea, and a complex neurodegenerative disorder), the relative timing and combination of these features was distinctive and expands the CTX clinical spectrum. Whereas patients with CTX typically develop cataracts in their second or third decade, our patient and her affected brother had congenital cataracts. Furthermore, intellectual impairment had been present since early childhood. This early onset of cognitive impairment is unusual in CTX, in which dementia usually occurs after the third or fourth decade. Diarrhea, which affects approximately 50% of patients with CTX and may be intractable, almost always begins before or simultaneously with neurologic symptoms. In contrast, our patient’s significant neurologic impairments began many years before diarrhea. Finally, magnetic resonance imaging findings in our patient were also somewhat unusual in that she exhibited confluent white matter changes suggestive of a leukodystrophy. Confluent leukodystrophy, although described before in patients with CTX, is not typical.

Recognition of CTX may be difficult because of its clinical heterogeneity and because the classic hallmarks (juvenile cataracts and tendon xanthomatosis) may be absent or appear only after neurologic signs are present. It is imperative to consider the diagnosis of CTX because of the treatability. Elevated plasma cholestanol level is diagnostic. The diagnosis of CTX should be considered and plasma cholestanol tested in all subjects with juvenile cataracts and in subjects with spasticity, early-onset dementia, ataxia, and parkinsonism of uncertain cause, particularly when associated with tendon xanthomas or diarrhea.

We found that 1 of 115 white control subjects was a carrier for this mutation (R362C). The control subject with this mutation (heterozygote) was not obviously related to the patient, although haplotype analysis to verify this was not performed. Estimates of the population frequency of the CYP27 R362C mutation in this ethnic group (white) would be more accurate by studying additional control subjects. Nonetheless, finding a carrier for the CYP27 mutation in this cohort was unexpected, given the apparent rarity of CTX in this population, and suggests that CTX may be more common than previously recognized. Given the observed frequency (8.7 × 10⁻³) and assuming random mating, the probability of 2 carriers of this CYP27 mutation mating would be 7.6 × 10⁻⁵.

Although our patient had many classic features of CTX (including cataracts, tendon xanthomas, diarrhea, and a complex neurodegenerative disorder), the relative timing and combination of these features was distinctive and expands the CTX clinical spectrum. Whereas patients with CTX typically develop cataracts in their second or third decade, our patient and her affected brother had congenital cataracts. Furthermore, intellectual impairment had been present since early childhood. This early onset of cognitive impairment is unusual in CTX, in which dementia usually occurs after the third or fourth decade. Diarrhea, which affects approximately 50% of patients with CTX and may be intractable, almost always begins before or simultaneously with neurologic symptoms. In contrast, our patient’s significant neurologic impairments began many years before diarrhea. Finally, magnetic resonance imaging findings in our patient were also somewhat unusual in that she exhibited confluent white matter changes suggestive of a leukodystrophy. Confluent leukodystrophy, although described before in patients with CTX, is not typical.

Recognition of CTX may be difficult because of its clinical heterogeneity and because the classic hallmarks (juvenile cataracts and tendon xanthomatosis) may be absent or appear only after neurologic signs are present. It is imperative to consider the diagnosis of CTX because of the treatability. Elevated plasma cholestanol level is diagnostic. The diagnosis of CTX should be considered and plasma cholestanol tested in all subjects with juvenile cataracts and in subjects with spasticity, early-onset dementia, ataxia, and parkinsonism of uncertain cause, particularly when associated with tendon xanthomas or diarrhea.

We found that 1 of 115 white control subjects was a carrier for this mutation (R362C). The control subject with this mutation (heterozygote) was not obviously related to the patient, although haplotype analysis to verify this was not performed. Estimates of the population frequency of the CYP27 R362C mutation in this ethnic group (white) would be more accurate by studying additional control subjects. Nonetheless, finding a carrier for the CYP27 mutation in this cohort was unexpected, given the apparent rarity of CTX in this population, and suggests that CTX may be more common than previously recognized. Given the observed frequency (8.7 × 10⁻³) and assuming random mating, the probability of 2 carriers of this CYP27 mutation mating would be 7.6 × 10⁻⁵.

Since CTX is a recessive disorder, approximately 25% of their progeny would be homozygous for this mutation (R362C) and develop CTX. This predicts that the prevalence of CTX (due to homozygosity of this mutation alone) among whites is approximately 1.9 per 100,000. Considering that there are many additional CYP27 mutations, the prevalence of CTX is estimated to be

With respect to the inheritance of CTX and the potential for carrier status, we performed a family study to identify the genetic cause of CTX in this patient. DNA samples from the proband, her parents, and their 10 siblings were obtained. DNA quality was assessed using standard protocols (data not shown). Sequence analysis of DNA from the proband’s parents showed that each parent was heterozygous (C and T) at this position. This mutation destroys an AciI restriction enzyme site. This was confirmed by restriction enzyme (AciI) digestion and 2% agarose gel electrophoresis using standard protocols (data not shown).

Restriction enzyme analysis of CYP27 exon 6 amplification products was performed in DNA samples from the 115 control subjects. One subject was found to be heterozygous for this mutation (results not shown). The heterozygous mutation was confirmed in this individual by DNA sequencing.

Figure 3. Representative CYP27 sequence from the patient and her parents’ DNA samples. The position of the CYP27 mutation R362C at complementary DNA position 1384 is indicated.
several-fold higher (3 to 5 per 100,000). These estimates predict that in the United States (population, >280 million) there are 8,400 to 14,000 individuals with CTX. This estimate is in striking contrast to the fewer than 100 cases reported worldwide. It is most likely that CTX is underdiagnosed. Greater recognition of this potentially treatable neurologic disorder is essential.

Accepted for Publication: May 6, 2005.
Correspondence: John K. Fink, MD, 5214 CCGCB, Box 0940, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0940 (jkfink@umich.edu).

Author Contributions: Study concept and design: Lorincz, Rainier, and Fink. Acquisition of data: Lorincz, Rainier, Thomas, and Fink. Analysis and interpretation of data: Lorincz, Rainier, and Fink. Drafting of the manuscript: Lorincz, Rainier, and Fink. Critical revision of the manuscript for important intellectual content: Lorincz, Rainier, Thomas, and Fink. Administrative, technical, and material support: Rainier, Thomas, and Fink. Clinical: Lorincz and Fink.

Funding/Support: This research was supported by grants K08NS45180 (Dr Lorincz), R01NS33645 (Dr Fink), and R01NS38713 (Dr Fink) from the National Institutes of Health, Bethesda, Md; the University of Michigan Institute of Gerontology, Ann Arbor (Dr Rainier); and a Merit Review Award from the Department of Veterans Affairs, Washington, DC (Dr Fink).

Acknowledgment: We are grateful to Lynette Girbach for expert secretarial assistance, and to the patients and their family members, without whom this investigation would not have been possible.

REFERENCES