CTX? NEVER HEARD OF IT: PART 2

How a single gene mutation can lead to pediatric cataract, diarrhea, and crippling neurologic disorders—and how optometrists can identify it early.

BY MEL FRIEDMAN, OD, FAAO

In the first article of this series (July/August 2017, *Advanced Ocular Care*),[1] I introduced CTX as a progressive, underdiagnosed, autosomal recessive genetic disease that is often first observed as pediatric cataracts by eye care providers.[2] In this article, we will continue to conversation about CTX by discussing its etiology, diagnosis, and management, and reviewing the disease's biochemical considerations—all of which are useful to know when encountering a patient with a possible diagnosis of CTX.

For those who feel as though this article is a biology lesson with little bearing on eye care, I encourage you to read the aforementioned part 1 of this article series.

GENENTICS

After it was identified as a disease in 1937, it took more than 30 years for the biochemical defect underlying the disease to be described.[3] In 1971, Salen reported that the biliary bile acid composition of CTX patients was abnormal, containing virtually no chenodeoxycholic acid (CDCA).[4] CDCA is one of the two primary bile acids—the other being cholic acid (CA)—that are normal constituents of bile.[4] Subsequently, the enzyme sterol 27-hydroxylase (encoded by the CYP27A1 gene) was thought to be defective in patients with CTX.[5] In 1994, the human CYP27A1 gene (CTX gene) was characterized, and analysis of many CTX patients showed that they had biallelic pathologic variants of the gene. These findings established CTX as a genetic disease affecting the biosynthesis of bile acids.[5] The CTX gene (CYP27A1), encodes the enzyme known as sterol 27-hydroxylase.[6] More than 80 different mutations related to CTX have been identified in this gene.[6]

CTX is inherited as an autosomal recessive disorder. In patients with CTX, both (CYP27A1) alleles (one inherited from each parent) have mutations which lead to the production of an abnormal sterol 27-hydroxylase enzyme.[7] The mode of inheritance of CTX may explain its rarity in the general population and why the disease in more prevalent in isolated populations (such as Jewish populations of Moroccan ancestry) and in communities where consanguineous marriages are common.

BIOCHEMISTRY

The normal sterol 27-hydroxylase enzyme (encoded by the CTX gene) helps to breakdown cholesterol to form the bile acids necessary for the body to digest and absorb fats and fat-soluble vitamins (vitamins A, D, E, and K). In patients with CTX, deficiencies of the fat-soluble vitamins are common along with the associated conditions such as osteoporosis (which may be due to vitamin D deficiency).[5]

Biosynthesis of the primary bile acids (CA and CDCA) is a complicated, multistep process.[8] The rate-limiting step in this process is catalyzed by another enzyme CYP7A1 (which is also a cytochrome P450 protein, related to sterol 27-hydroxylase which is abnormal in CTX patients).[8,9] Most of the bile acids secreted (as bile) into the gastrointestinal tract are reabsorbed and transported back to the liver to be reused via an enterohepatic circulation.[10,11] This circulation conserves the amount of bile acids so that only small amounts of bile acids need to be made anew every day. The primary bile acids also regulate their own production from cholesterol through a negative feedback mechanism. When the levels of the bile acids drop, the liver responds by synthesizing more bile acids and when the level rises, the production of bile acids by the liver is decreased via

CTX, a disease often first noticed by optometrists, can be treated. First, however, clinicians need to know the ins and outs of the disease pathway.

the inhibition of the rate-limiting enzyme (CYP7A1) by CDCA. CDCA is more potent than CA at inhibiting this rate-limiting enzyme.[12]

Malfunctioning sterol 27-hydroxylase enzyme damages the body's capacity to break down cholesterol into bile acids. Consequently, CTX patients have significantly increased levels of (the precursors of bile acids), the bile alcohols including cholestanol (not cholesterol). In CTX large amounts of these excess bile alcohols (not bile acids) including cholestanol, accumulate in the brain, peripheral nerves, and tendons—as well as in the lenses, resulting in cataract development. The accumulation of cholestanol and the other bile alcohols (which are thought to be toxic) is probably responsible for the signs and symptoms of CTX.[12]

PRESENTATION OF DISEASE

There is no typical clinical presentation of CTX and the presentation may be age-dependent. In childhood and adolescence, for example, chronic diarrhea is a more common presentation, as are bilateral cataracts (Figure 1). In the second and third decades of life, xanthomas (Figure 2) and nervous system dysfunction commonly present. The most serious problem with CTX is the damage to the nervous system. This damage is time-dependent. It is imperative that the disease is identified early in the life of a patient with CTX; commonly, and optometrist is the first to encounter a pediatric patient with bilateral cataract. Currently, the average age at diagnosis about 35.5 years. This represents a delay of about 20 years from when symptoms appear to the time of diagnosis. At age 35, the nervous systems of patients with CTX may have sustained irreversible damage.[13]

In approximately 75% of individuals affected by CTX, cataracts are the first finding, often appearing in the first decade of life.[13] The cataracts initially present as flecks (zonular cortical opacities containing cholestanol)[5] in the lenses and rarely affect vision, and many clinicians may consider them harmless. These flecks (Figure 1) have been reported in the literature in patients as young as 18 months.[14]

CONFIRMING DIAGNOSIS

The diagnosis of CTX is confirmed when the clinical picture that has been previously described is supported by laboratory tests. There are two lab tests for confirming the diagnosis of CTX: a genetic test and blood test.

Genetic testing can identify the two allelic pathogenic variants of CYP27A1, which could be the basis for diagnosis of CTX. A blood test to measure levels of cholestanol is also needed to confirm the diagnosis.[13] In a patient without CTX, trace quantities of cholestanol are present in the plasma (approximately 330 ±30 µg/dL); in CTX patients, cholestanol levels are about 5 to 10 times above the normal range. The levels of cholestanol are also used to assess a patient's response to treatment. In responsive patients, the levels of plasma cholestanol may return to normal levels within a year of therapy. This may also be accompanied by improvements in other symptoms and signs of the disease.[13,15]

There are only a few diagnostic labs in the United States offering plasma cholestanol testing. However, patients who are suspected of having CTX can now be tested for plasma cholestanol at no cost to the patient. Visit www.TestCTX.com for information on the free cholestanol test. If the test is positive, the patient should be immediately referred a specialist who manages CTX patients.

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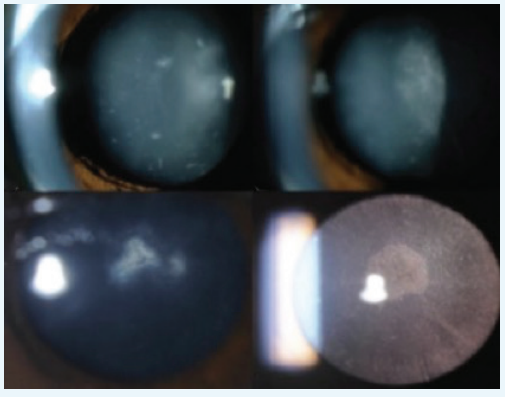

Figure 1. Patients with CTX commonly present with bilateral cataract at a young age. Some patients demonstrate zonular cortical opacities containing cholestanol, which, although apparently nonthreatening, should signal to the clinician that such patients be tested for CTX.

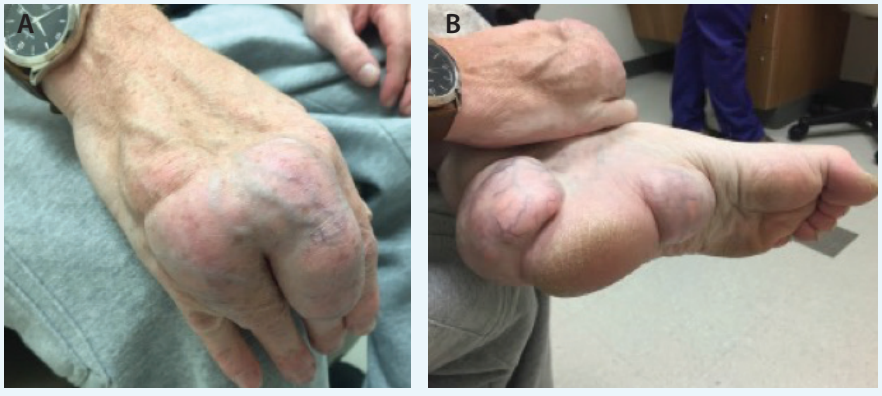

Figure 2. Xanthomas on the hands (A) or feet (B) commonly present in patients with CTX who are in their teens and 20s.

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MANAGING CTX

Patients with CTX are cared for by the appropriate specialist depending on their clinical presentation. A patient with central nervous system dysfunction should, for example, be appropriately managed by a neurologist. In all patients, improvement of clinical symptoms and or decrease in cholestanol levels over time indicate responsiveness to treatment.[13]

The drug treatment of CTX involves the replacement of one or both primary bile acids (CA and CDCA) which patients with CTX cannot biosynthesize.[15] CA capsules (Choblam, Retrophin) are approved for the treatment of CTX by the US Food and Drug Administration (FDA). Synthetic CDCA (Chenodal, Retrophin) is approved by the FDA for the dissolution of gallstones. Though CDCA is not approved for the treatment of CTX, the FDA has said that that drug is medically necessary for the treatment of CTX.

It has been shown that CDCA is 14 times less abundant than CA in patients CTX. Because it is the more potent inhibitor of the rate-limiting enzyme CYP7A1 and theoretically more effective in the treatment of CTX, CDCA may shut down the production of bile alcohols such as cholestanol which are thought to be responsible for the pathology and clinical presentation of CTX.[15] ■

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