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COMMENTARY

Living with Cerebrotendinous Xanthomatosis: Patient, Caregiver, and Expert Perspectives

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ABSTRACT

In this article, patients with cerebrotendinous xanthomatosis (CTX) and caregivers detail their experience with lifelong symptoms, diagnosis, treatment and efficacy, and ongoing disease management. One patient and four caregivers describe the challenges associated with pursuing a correct diagnosis for years before testing confirmed a CTX diagnosis. They also detail their ongoing struggles and desire for greater access to physicians with CTX knowledge and to reliable online resources to continue their education about the disease and strategies for symptom management. The expert perspective is a direct response by three CTX researchers, including physicians who are treating patients with CTX in the United States and experts whose laboratories provide genetic and biochemical testing for CTX. They respond to many of the patient and caregiver concerns, including steps that are being taken to identify CTX earlier and provide access to confirmatory diagnostic testing sooner, and suggest the best online resources for CTX-related information and access to webinars and support groups. While the expert perspective is a direct response to the patient and caregiver authors' CTX journeys, it should be beneficial to any patient with CTX or their caregivers.

Keywords: Cerebrotendinous xanthomatosis; CDCA; Chenodeoxycholic acid; CTX; *CYP27A1*

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Key Summary Points

Cerebrotendinous xanthomatosis (CTX) is a rare bile acid synthesis disease that causes a myriad of symptoms, including progressive neurological deterioration if left untreated.

The varied symptomology and rarity of the disease make diagnosis challenging, delaying diagnosis and treatment.

Here, patients and caregivers detail the diagnostic challenges and ongoing struggles of living with CTX and an expert perspective provides researchers and physicians an opportunity to directly address patient and caregiver concerns.

Few if any publications give those directly affected by CTX the opportunity to detail what it is like living with CTX.

We believe that their concerns are shared by the broader CTX community, and the expert perspective provides valuable information that the CTX community would find beneficial.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive bile acid synthesis disorder caused by biallelic pathogenic variants in *CYP27A1*, the gene that codes for sterol 27-hydroxylase [1]. In the liver, sterol 27-hydroxylase is crucial for normal cholesterol metabolism and bile acid synthesis [1]. Patients with CTX have disrupted bile acid synthesis, which leads to elevated bile acid pathway intermediates that are converted to cholestanol and bile alcohols [1]. Elevated blood cholestanol and urine bile alcohols are a hallmark of CTX, along with varied symptomology, including chronic early-onset diarrhea, early-onset bilateral cataracts, tendon xanthomas, and neurological deterioration [2, 3]. Case reports of patients with CTX show that quality of life is adversely affected in both patients and their families [4–6]. The current accepted treatment for CTX is chenodeoxycholic acid (CDCA), which has been shown to reduce blood cholestanol and urine bile alcohol levels and improve symptoms [4].

Here, patients and caregivers detail their experiences living with CTX. Along with background information regarding symptom onset, time to diagnosis, and treatments, patients and caregivers identify areas that could be improved upon for this rare disease to help them and their health care providers (HCPs) make better decisions about diagnosis, care, and disease management. The expert perspective is a direct response from the CTX expert researchers who have authored this paper, including physicians treating patients with CTX and experts whose laboratories perform genetic and biochemical testing for CTX. Patients and caregivers completed informed consent forms, indicating that they are aware that personal medical information will be disclosed to the public. Pseudonyms were used for patients and caregivers who were unwilling to disclose their identity, and details of their medical information were pseudoanyonymized.

PATIENT AND CAREGIVER PERSPECTIVE

Caregiver 1

My daughter was diagnosed with CTX at 8 years old. She struggled with persistent diarrhea as a child but hit all of her developmental milestones and excelled in school until first grade. At 7 years old, she developed a tremor in her hands, which prompted us to visit the pediatrician. She deteriorated rapidly in the next 18 months. She could no longer count to 100 or read without losing her place. She was unable to tie her shoes, put toothpaste on her toothbrush, or dress herself. She started having daily falls due to ataxia and pain in her legs from peripheral neuropathy. She was unable to walk through a grocery store without being placed in the shopping cart. She had intense brain fog

and often seemed like she was unaware of what was going on around her. During that time, we saw pediatricians, neurologists, and geneticists at three different facilities. She underwent intense testing because of the neurological nature of her symptoms and her rapid deterioration. She was confirmed to have CTX via genetic testing after 18 months of seeking a diagnosis. Follow-up testing for her two brothers showed that one had CTX and the other was neither affected nor a carrier.

My son had prolonged jaundice at birth and was an inpatient for two weeks as a newborn. In his first few years, he had persistent diarrhea but was seemingly healthy otherwise. We stopped seeking medical attention after we were told that chronic diarrhea was normal for breastfeeding babies and for toddlers transitioning to solid foods. As he got older, we eliminated possibly sensitive foods but with little success. In fifth grade, he developed social problems like making eye contact and connecting with other people. He also developed facial and vocal tics, which we were told weren't uncommon in young boys. In middle school, he developed behavioral problems. It was at this time that his sister was diagnosed with CTX and we suspected his symptoms were likely CTX. Subsequent genetic testing confirmed his diagnosis.

Both children began treatment with CDCA 125 mg 3 times daily immediately after diagnosis. Liver function and cholestanol levels were checked monthly for the first 3 months, then every 6 months. After 3 months, my daughter's cholestanol levels were within normal range. For my son, his cholestanol levels increased in the first 3 months. After consulting with our CTX specialist and other patients on a CTX Facebook group we started, we tried taking CDCA with food. Soon after, our son's cholestanol levels lowered.

After 6 months of CDCA treatment, I noticed improvement in both children's symptoms. They both reported less brain fog, which was confirmed by teachers at school. My daughter's tremors improved, as well as her ataxia and pain in her legs. She still suffers from autonomic dysfunction, learning disabilities, peripheral neuropathy, tremors, severe anxiety, and sensory processing problems. My son, who was diagnosed at an older age, has continued to display autistic-like behaviors, tics, obsessive compulsive disorder, moderate anxiety, and severe depression, including suicidal thoughts. Both children continue to struggle with persistent diarrhea, though it has improved with treatment. They each had cataracts removed 1 year after starting treatment. They have also put on a considerable amount of weight over the years since starting treatment and are now within normal height and weight. Now that both children are at adult height and weight, their CDCA dose has increased to 250 mg 3 times daily.

Both children are monitored by their neurologist and neuropsychologist yearly when cholestanol levels and liver function are measured. There has been conflicting information on how often lab testing and magnetic resonance imaging (MRI) should be taken. We have decided not to take MRIs regularly because we felt it is better for their mental health to minimize clinical/invasive procedures unless necessary. However, we continue with regular neuropsychological testing, as this has been extremely helpful in getting them the necessary support at home and at school.

My husband and I have become parent advocates for CTX, and are thus able to keep up with new information in the CTX community. This has helped us connect with other CTX-affected families and share experiences. We have heard much about autistic behaviors and psychological problems in children and teenagers with CTX. However, we have not seen much discussion of autistic behaviors in patients with CTX in the scientific literature to date. CTX literature tends to focus on adult patients and therefore focuses on mobility issues and neurological deterioration, perhaps overlooking the psychological and behavioral impact of CTX. We try to attend at least a United Leukodystrophy Foundation (ULF) or Hunter's Hope conference yearly to connect with more patients and families. We're advocates for CTX Alliance, whose aim is to compile information from both CTX specialists and families affected by CTX into one online resource.

Caregiver 2

My child was diagnosed with CTX as a teenager after struggling with symptoms for over 10 years. My child was athletic and social until age 5. We saw a developmental pediatrician who prescribed a blood pressure medication off label to calm my child but did not treat the lack of focus, so schoolwork suffered. We saw sustained improvements with speech therapy, but the improvements made in physical and occupational therapy were lost within months. Soon after, a psychologist diagnosed my child with Asperger's syndrome and prescribed a medication to help focus. The psychologist was helpful and my child continues to see him. After seeing a play therapist who ordered in-depth educational testing, my child was diagnosed with a nonverbal learning disorder. In third grade, my child struggled to stay calm and remain in school and performed poorly on tests. As a preteen, my child lost the ability to run and jump, struggled socially with only a few friends, and continued to struggle in school. As a teenager, my child's triglycerides were very high and doctors identified metabolic waste products in the blood. At the time, we thought this may be related to a metabolic disease for which we already knew my child was a carrier. We were referred to a geneticist who confirmed the CTX diagnosis. Biochemical testing showed urine bile alcohols were extremely elevated and blood cholestanol levels were high. Soon after, brain MRIs showed significant white matter deposits. My child began receiving treatment with CDCA, which has somewhat improved the cognitive symptoms and normalized cholestanol levels. My child has osteopenia despite calcium and vitamin D supplementation and low alkaline phosphate and also receives a mood stabilizer. The journey to get a correct diagnosis was a long and difficult road where we continually had to push for more tests when the current diagnosis and treatment failed. Today, I wish we had better access to neurologic and psychiatric support and to CTX-related information online, including anecdotes from other patients and families living with CTX regarding their symptom management strategies.

Caregiver 3

My husband was diagnosed with CTX at 32 years old after struggling with tendon xanthomas and coordination and balance issues for over 10 years. After running track in high school, he began experiencing balance issues while riding a bike or roller-skating at 19 years old. He slowly developed Achilles tendon xanthomas and an abnormal gait with toe drop over the next several years. At 28 years old, he experienced severe depression, and his psychologist encouraged him to pursue a diagnosis for his xanthomas and loss of balance. A neurologist diagnosed him with multiple sclerosis (MS) after studies showed decreased nerve conduction in his extremities and lesions in the white matter of the brain. Follow-up with a neurologist who specialized in MS lead to my husband being diagnosed with Stiff Man Syndrome. We saw an orthopedic ankle specialist for his xanthomas who referred us to an endocrinologist after biopsy. With my husband's varied symptomology, the endocrinologist suspected CTX. After blood and family genetic testing, my husband's CTX was confirmed. He receives treatment with CDCA 200 mg 4 times daily and also receives cholesterol-lowering, anti-anxiety, and anti-depressive medication. His mental clarity greatly improved in the first year of CDCA treatment. His gait has since worsened, and his xanthomas and memory issues persist. He sees his CTX specialist yearly and has cholestanol levels measured every few years. Despite receiving the maximum daily dose of CDCA, my husband's cholestanol levels are still slightly elevated.

At the time he was diagnosed, over 25 years ago, we made do with the online resources available, which wasn't much. We had to advocate for our own care and constantly pushed HCPs for more testing. Today, we worry about the availability and cost of his medication. We don't know if Medicare covers his CTX medication and worry about the financial hardship his treatment could cause. I wish we had access to more psychiatric support and ambulatory support since my husband has limited mobility. We consult CTX Alliance often and attend ULF conferences. Access to

more information both online and with HCPs who are aware of this debilitating disease would be beneficial.

Caregiver 4

My sister was diagnosed at 35 years old after dealing with CTX symptoms, such as bilateral juvenile cataracts, cognitive impairment, mood disorders, musculoskeletal weakness, and behavioral changes since childhood. We pursued a diagnosis for over 15 years with neurologists, psychiatrists, and cardiologists, among others, without ever undergoing genetic testing, which resulted in multiple misdiagnoses. Once diagnosed with CTX, she started treatment with CDCA 250 mg 3 times daily and also receives Armour® Thyroid. While we've seen improvement and stabilization in CTX symptoms, her delayed diagnosis has resulted in progressive, irreversible musculoskeletal and neurocognitive impairment. She currently sees a neurologist and receives standard blood tests every 6 months. We do not routinely monitor her plasma cholestanol levels because it is difficult to get the test ordered. Because our neurologist is part of an academic teaching hospital, we routinely see rotating training physicians who must be educated about our situation. Thus, it is difficult to maintain continuity of care, advocate for her treatment and blood testing, and identify non-pharmacological therapeutic options. We have continued to educate ourselves about living with CTX by consulting websites such as Orphanet, National Organization for Rare Disorders (NORD), and scientific publications. From our experience, I believe the CTX community could benefit from more psychiatric support, opportunities to meet other CTX-affected individuals and their families, and better information online.

Patient 1

As a child and teenager, I suffered from persistent diarrhea that was so common it became normal. At age 19, I was diagnosed with bilateral cataracts that required surgery. At age 26, a xanthoma developed on my left hand that was removed soon after. My surgeon suspected I may have CTX. One year later, at age 27, I was diagnosed with CTX after blood tests showed elevated cholestanol levels. I started receiving treatment with CDCA 250 mg 3 times daily, which helped my diarrhea symptoms. My plasma cholestanol levels are now routinely monitored every 6 months and are stable and normal. I experienced no adverse events of CDCA treatment. I still have a few small xanthomas, but they've stabilized. I also experience balance issues occasionally, and my gait when I walk is slightly abnormal. I visit my ophthalmologist yearly to check my eyes, and wish I had better access to eye doctors with CTX knowledge. Looking back, if I was diagnosed with CTX sooner, perhaps treatment could have slowed or halted the onset of cataracts. I think patients with CTX and their families could benefit from more access to CTX-related information online and more opportunities to meet other CTX-affected individuals and their families.

Expert Perspective

The long diagnostic journey detailed above is unfortunately common in our experience for patients and families affected by CTX. It is common for patients to wait 25 years from the first onset of CTX symptoms until a definitive etiological diagnosis [1, 3]. Diagnosing CTX is difficult due to its varied symptomology, which HCPs often attribute, understandably, to more common conditions. In the case of the children of Caregiver 1, childhood chronic diarrhea was thought to be related to breastfeeding infants or toddlers transitioning to solid foods. Neurologic CTX symptoms were misdiagnosed as MS in the case of Caregiver 3's husband, and developmental delay associated with CTX was diagnosed as autism spectrum disorder (ASD) in the case of Caregiver 2's child, initially without attempts to identify the etiological diagnosis responsible for the autism. ASD has historically been less recognized as a symptom of CTX and therefore delayed proper diagnosis. In the last decade, we have recognized that, despite most CTX diagnoses occurring in adulthood, a

number of CTX symptoms may be present in pediatric patients [7]. A recent study of 77 patients with CTX identified 10 patients with ASD, 9 of whom were pediatric patients [8]. In all but one case, the CTX diagnosis was made after the ASD diagnosis. Early detection of CTX and treatment initiation prior to the onset of irreversible symptoms is likely associated with better outcomes for patients [5, 6]. As more pediatric patients are identified through our efforts to diagnose CTX earlier, we can better characterize CTX symptomology in children and initiate treatment sooner.

To that end, researchers are now identifying populations who are more likely to have CTX based on their symptomology to ensure that patients with CTX will be diagnosed earlier. Bilateral cataracts are present in up to 88% of patients with CTX and, in the patient and caregiver self-reports above, were present in two cases [9]. The prevalence of CTX in patients with early-onset bilateral cataracts is 1 in 100, far higher than the estimated CTX prevalence of 1 in 44,000–3,400,000 in the general population [9, 10]. In the case of Patient 1, she presented with cataracts at 19 years old and was not diagnosed with CTX until she developed xanthomas nearly 10 years later. As we identify at-risk populations like those with early-onset bilateral cataracts, increased CTX awareness by specialists can help to identify those affected like Patient 1 sooner.

Pediatricians, dermatologists, cardiologists (especially preventative cardiologists), lipidologists, dermatologists, and endocrinologists can play an important role in diagnosing CTX by identifying tendon xanthomas, a common early symptom of CTX. Xanthomas are also a symptom of familial hypercholesterolemia (FH), an autosomal dominant condition characterized by life-long elevated blood cholesterol and increased risk of cardiovascular disease [11]. Tendon xanthomas in childhood are typically associated with homozygous FH, whereas patients with heterozygous FH typically develop xanthomas in adulthood [11, 12]. In children, xanthomas are often the reason parents seek medical attention before an FH diagnosis [12]. Patients with CTX typically have normal blood lipids (on routine testing) but have elevated cholestanol. In patients presenting with tendon xanthomas in the absence of elevated blood lipids, a CTX diagnosis should be pursued via blood cholestanol measurement and genetic testing.

Caregiver 3 described her experience advocating for her husband's care and pushing for further testing, a problem that is common in diagnostic journeys of patients with CTX. Prior to the last decade, a CTX diagnosis required specific clinical suspicion and CTX awareness by the physician. Clinical suspicion of CTX is difficult for HCPs because of the wide spectrum of CTX symptomology and the rarity of the disease. Most HCPs will never have cared for a patient with CTX in their career. This means that, too often, a CTX diagnosis is delayed, often by years, as was the case with Caregiver 3's husband. Today, *CYP27A1* has been added to many genetic testing panels that are being used increasingly by HCPs to identify underlying causes of bilateral cataracts, cholestasis, ASD, and other symptoms. Large gene panels, whole exome or whole genome sequencing, and other hypothesis-free diagnostic tests can detect rare CTX-causing genetic variants, and serve as a "safety net" for physicians who do not have suspicion for a specific rare disease but believe there may be an occult condition.

While large gene panels can help reduce the CTX diagnostic delay in symptomatic patients, newborn screening would eliminate the delay by allowing for diagnosis and initiation of CDCA therapy as early as possible. In 2018, CTX was nominated to be considered for inclusion on the Recommended Uniform Screening Panel, a standardized list of disorders for which the US Department of Health and Human Services (DHHS) recommends all newborns should be screened [13, 14]. The Advisory Committee on Heritable Disorders in Newborns and Children to the Secretary of DHHS responded to the nomination by requesting the detection of at least one identifiable CTX case though a prospective newborn screening study before CTX will be considered for addition [13, 14]. Efforts by researchers and the CTX community are underway to generate the evidence requested by the Advisory Committee. We feel that the existing published literature supports the

contention that CTX is an appropriate disease for inclusion in newborn screening programs. Newborn screening assays are available for newborn screening using instrumentation already available in state newborn screening laboratories and amenable to multiplexing testing with other disorders currently included in routine state newborn screening testing [15, 16].

Caregiver 4 described the difficulty accessing biochemical testing for CTX and Caregiver 1 described conflicting information on how often biochemical testing should be performed after treatment initiation. In the US, specific biochemical testing for CTX is currently only offered by three laboratories. Biochemical testing (at minimum blood cholestanol and urine bile alcohol) should be used to confirm a diagnosis of CTX. Periodic biochemical testing is indicated after initiating CDCA treatment, which is helpful for assessing treatment efficacy, dosing, and treatment adherence. After cholestanol normalizes, biochemical testing is typically performed every 6–12 months. More frequent testing is indicated if there is any change in clinical status [17].

Most patients and caregivers described their self-education efforts to research CTX and would like to see more online resources available that provide reliable information on treatments and disease management and opportunities to meet other CTX-affected individuals and their families. Currently, the best online resources are the patient advocacy groups CTX Alliance (https://ctxalliance.org/) and ULF (https://ulf.org/). There, patients can find information about their disease, treatment, patient support groups, and scientific publications, and search for specialists with CTX experience. ULF hosts support group webinars for both patients and caregivers, and a yearly family conference that provides attendees access to the latest information from physicians and researchers. Numerous social media support groups have been started and are a great way to connect with other patients and families affected by CTX. Living with CTX is a lifelong challenge, but expert physicians, researchers, and advocates are working to identify patients with CTX earlier, identify better treatments, and provide patients, caregivers, and HCPs with resources to better understand the disease and how to manage it.

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