Cerebrotendinous Xanthomatosis Presenting with Infantile Spasms and Intellectual Disability

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Abstract Cerebrotendinous xanthomatosis (CTX) is an inborn error of metabolism leading to progressive multisystem disease. Symptoms often begin in the first decade of life with chronic diarrhea, cataracts, developmental delay, intellectual disability, and cerebellar or pyramidal dysfunction. Later manifestations include tendon xanthomas, polyneuropathy, and abnormal neuroimaging. Pathogenic biallelic variants in *CYP27A1* leading to compromised function of sterol 27-hydroxylase result in accumulation of detectable toxic intermediates of bile acid synthesis rendering both genetic and biochemical testing effective diagnostic tools. Effective treatment with chenodeoxycholic acid is available, making early diagnosis critical for patient care. Here we report a new patient with CTX and describe the early signs of disease in this patient. Initial symptoms included infantile spasms, which have not previously been reported in CTX. Developmental delay, mild intellectual disability with measured cognitive decline in childhood, was also observed. These clinical signs do not traditionally

compel testing for CTX, and we highlight the need to consider this rare but treatable disorder among the differential diagnosis of children with similar clinical presentation. Increased awareness of early signs of CTX is important for improving time to diagnosis for this patient population.

Introduction

Cerebrotendinous xanthomatosis (CTX, OMIM 213700) is an autosomal recessive disorder of bile acid synthesis that manifests as a progressive, multi-system disease. Biallelic pathogenic variants in the gene *CYP27A1* cause deficiency of the enzyme produced by *CYP27A1*, sterol 27-hydroxylase, resulting in the accumulation of cholesterol, cholestanol, and other intermediates in tissues and the pathology that characterizes CTX (Panzenboeck et al. 2007). Elevated cholestanol in serum and elevated urine bile alcohols are characteristic diagnostic findings in patients with CTX. The clinical features of CTX vary widely, even within families. Bilateral cataracts are one of the most common features of CTX and are usually noted in the second decade of life, though the age of onset is variable (Cruysberg et al. 1995; Mignarri et al. 2014; Degos et al. 2016). Other common pediatric manifestations of CTX include intellectual disability or developmental delay (60% of patients, mean age of 6 years at diagnosis) and epilepsy (33% of patients, mean age of diagnosis 10 years) (Mignarri et al. 2014). Chronic diarrhea may begin in infancy and continue into adulthood (Verrips et al. 2000). Rarely, cholestatic liver disease of infantile onset has been reported (Clayton et al. 2002). Cerebellar and pyramidal signs also appear in

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childhood with polyneuropathy typically developing in the third or fourth decade of life. The most common abnormality on magnetic resonance imaging (MRI) of the brain in CTX is T2 hyperintensity of the dentate nuclei of the cerebellum (Barkhof et al. 2000). The tendon xanthomas for which CTX is named do not typically appear until much later in the course of the disease if at all (Mignarri et al. 2014).

The largest reported case series of CTX patients consisted of 55 patients (Mignarri et al. 2014). The mean age at diagnosis was 35 years with mean age of onset of symptoms at 9 years, implying that delays to diagnosis are significant and that opportunities for early treatment initiation have historically been missed. The incidence of CTX is not known, but recent estimates range from 1:134,970 to 1:461,358 in Europeans and even higher in Asians (~1:70,000), also supporting the notion that some cases may go undiagnosed (Appadurai et al. 2015). Noninvasive testing of cholesterol metabolites and bile acid intermediates facilitates diagnosis of CTX. In addition, 7 α -hydroxy-4-cholesten-3-one (7 α 4C) is helpful in diagnosis and monitoring of treatment for CTX. Serum levels of 7 α 4C are more significantly elevated in individuals with CTX than other metabolites, and 7 α 4C levels exhibit dramatic responses to treatment (Mignarri et al. 2016). 7 α 4C crosses the blood-brain barrier more efficiently than cholestanol and may be a significant contributing factor to pathogenesis in the central nervous system (Panzenboeck et al. 2007).

Treatment is available for CTX that is effective at remediating symptoms and, if started in childhood, can prevent clinical manifestation of the disease (Berginer et al. 2015). Thus, the identification of individuals with CTX at a young age significantly benefits patients and families. Given the importance of early diagnosis and initiation of treatment, we report here a case of CTX presenting with infantile spasms, highlighting the need to consider this rare but treatable disorder among the differential diagnosis of children presenting with seizures, even in the first year of life.

Materials and Methods

Molecular Genetic Testing

CYP27A1 sequencing was performed by Baylor Miraca Genetics Laboratory (Houston, TX) using next-generation sequencing methods and confirmed using Sanger sequencing. The detected pathogenic variant was submitted to the Leiden Open Variation Database by the authors.

Biochemical Testing

Cholestanol testing was performed by the Kennedy Krieger Institute (Baltimore, MD). Serum bile acid metabolite levels were performed by Baylor Miraca Genetics Laboratory (Houston, TX). Urine bile alcohol testing was performed by Cincinnati Children's Hospital (Cincinnati, OH).

Imaging

MRI of the brain was performed using standard clinical protocols and images were reviewed by a pediatric neuro-radiologist.

Cognitive testing

Cognitive testing was performed on a clinical basis by a licensed neuropsychologist.

EEG

EEG with video was performed using standard clinical protocols and was reviewed by board-certified epileptologists.

Results

The patient, a Caucasian female, was the first live birth to a 30-year-old mother who had one prior pregnancy. Regular prenatal care was obtained, and there were no concerns for exposures during the pregnancy. The patient was born at term via normal spontaneous vaginal delivery and did not require neonatal resuscitation, though nasal fracture was noted on initial exam. Early growth and development were appropriate, and the patient initially presented at 4 months with clusters of tonic extensor spasms. Brain MRI at that time was normal. Routine electroencephalogram (EEG) showed hypsarrhythmia (>300 μ V) with multifocal discharges and electrodecrements without clinical accompaniment. She was treated with adrenocorticotrophic hormone (ACTH, 20 units injected daily for 4 weeks) followed by zonisamide for a diagnosis of infantile spasms. Repeat EEG at 7 months of age was normal. She also had infantile torticollis and resultant positional plagiocephaly. She did not have additional clinical seizures after ACTH administration, and zonisamide treatment was discontinued after 1 year of therapy. Prolonged overnight EEG at 6 years demonstrated slowing of the occipital dominant rhythm, and multifocal epileptiform discharges of low voltage and frequency but no seizures were captured.

The patient required treatment for constipation and had nocturnal enuresis until age 6 years. Developmental concerns prior to the initiation of schooling consisted of mildly abnormal speech articulation, clumsiness with occasional falls, and difficulty with fine motor tasks such as handwriting and buttoning clothing. Upon enrollment in kindergarten, the patient was unable to complete grade-level work. Repeat MRI of the brain was again unremarkable. At age 8 years, the Wechsler Intelligence Test for Children IV (WISC-IV) was administered with a full scale intelligence quotient (FSIQ) of 75. There were specific concerns for poor executive function out of proportion to other deficits. Neuropsychological testing was repeated at age 12 years, and FSIQ on the WISC-IV was found to be 63, which is a one standard deviation decrease from the previous testing. Verbal skills were strong but memory and reasoning were weak.

The patient failed a routine vision screen at age 12 and was referred to an ophthalmologist. She was diagnosed with cataracts and underwent bilateral lens extraction with intraocular artificial lens implantation. Given her history of developmental regression and bilateral cataracts, serum cholestanol level was obtained and found to be 20.39 µg/mL (normal <3.71 µg/mL). Urine bile alcohols showed elevated polyhydroxylated bile alcohol glucuronides. Molecular genetic testing showed an apparently homozygous variant in *CYP27A1* (NM_000784): c.1016C>T (p. Thr339Met), an allele which has previously been reported in other patients with a clinical and biochemical diagnosis of CTX (Reshef et al. 1994; Gupta et al. 2007). MRI of the brain showed faint T2 hyperintensities of the cerebellar dentate nuclei bilaterally. On physical examination at age 12, the patient had hyperactive deep tendon reflexes, increased muscle tone of the lower extremities with mild contractures at the knees and ankles, mild ataxia, no evidence of sensory neuropathy, and no evidence of tendon xanthomas. Serum aspartate aminotransferase (AST) was mildly elevated at the time of diagnosis, 38 units/L (normal <31 units/L).

The patient was started on CDCA 500 mg daily and after 1 month, cholestanol level decreased to 10.34 µg/mL (Table 1). Serum bile acid profile performed at that time showed 7αC level of 2.51 µmol/L (normal <0.05 µmol/L). CDCA was increased to 750 mg daily and studies were repeated after 6 months at that dose. Cholestanol level decreased to 3.31 µg/mL. 7αC level decreased to 0.47 µmol/L. The patient has tolerated CDCA therapy well without gastrointestinal discomfort. AST remained mildly elevated with CDCA treatment at 32 units/L. There was mild elevation of alanine aminotransferase (ALT) from 21 to 44 units/L (normal <31 units/L) with CDCA treatment. Aminotransferase levels have been monitored due to the known risk of

Table 1 Plasma biochemical markers show response to CDCA treatment

	Cholestanol (µg/mL)	7αC4 (µmol/L)
Normal	<3.71	<0.05
Pretreatment	20.4	–
CDCA, 500 mg	10.3	2.5
CDCA, 750 mg	3.3	0.5

hepatotoxicity with CDCA treatment (Huidekoper et al. 2016).

The patient has one healthy sibling and one sibling with autism. Her mother has well-controlled adult-onset epilepsy. These three unaffected family members have normal serum cholestanol concentration. The mother and father were both found to be heterozygous for the *CYP27A1* pathogenic variant, confirming that the patient has two pathogenic alleles *in trans*. The patient's father has cataracts due to adult-onset glaucoma.

Discussion

We report a new case of CTX with infantile spasm, developmental delay, intellectual disability, and pediatric cognitive decline. CTX is a multisystem degenerative disease that is usually diagnosed after a protracted delay from initial symptomatic onset due to nonspecific early symptoms, variable clinical presentation, and a course that typically progresses over decades. Given that effective treatment is available and can prevent disease progression, diagnosis is critically important for patients and greater awareness of the disease and earliest manifestations beneficial. Cataracts are the most commonly occurring pediatric sign, with an average age of onset in the second decade of life. Importantly there are also earlier clinical symptoms that present in the first decade of life with significant frequency. Two-thirds of patients have intellectual disability or developmental delay, and one-third of patients with CTX are diagnosed with epilepsy, including a small number of patients with epilepsy very early in life (Pedroso et al. 2012; Kauffman et al. 2012; Mignarri et al. 2014). Chronic diarrhea can be one of the earliest clinical signs of CTX that appears in less than half of cases (Mignarri et al. 2014).

The number of known genetic etiologies of infantile spasms has increased dramatically in recent years with the advent of chromosomal microarray, large sequencing panels, and whole exome sequencing (Michaud et al. 2014; Paciorkowski et al. 2011). To date, *CYP27A1* has not been reported in published cohorts of patients with

infantile spasms who have undergone broad molecular genetic testing. This implies that, while important to include in the differential for this patient population, CTX is unlikely to be a common diagnosis in this setting. The patient reported in this paper had normal chromosomal microarray, but did not have whole exome sequencing after diagnosis of CTX to evaluate for additional genetic etiologies of infantile spasms. We cannot exclude the possibility that there is a second unrelated etiology of infantile spasms for this patient since there are no available tests with 100% sensitivity to detect all possible causes of seizures and developmental delay, not even whole exome sequencing. However, since the time of her initial seizures, she has had progressive features of CTX including development of cataracts, dentate nucleus MRI abnormalities, ataxia, and lower extremity spasticity. Importantly, there have not been any additional findings that are inconsistent with CTX, leading to our conclusion that CTX is the most likely etiology of her infantile spasms.

Therapy consists of decreasing synthesis of toxic bile acid intermediates to provide negative feedback on the pathway. Multiple studies have reported clinical efficacy of CDCA in CTX including lengthy longitudinal studies after initiation of therapy. Importance of early initiation of therapy was emphasized by a recent report of 18 patients with up to 23 years on CDCA therapy in which there was a correlation between early age at initiation of CDCA therapy and improved neurological outcomes (Yahalom et al. 2013). There are fewer reports of outcomes during childhood with CDCA treatment of those that become symptomatic at an early age. In a report of five patients treated with CDCA, two of three patients that had developmental delay in childhood showed improvement of 10 points or more on intelligence quotient testing after 2 years of treatment (Van Heijst et al. 1998). Four members of one family were treated with CDCA, and the two children that were asymptomatic at the time of initiating treatment remained so 14 years later (Berginer et al. 2009).

This case emphasizes the importance for neurologists, ophthalmologists, gastroenterologists, and geneticists to maintain a high index of suspicion for CTX in the setting of consistent clinical features. In light of the availability of CDCA as a specific and effective treatment, clinicians should consider testing for CTX with biochemical assays or sequencing of *CYP27A1* when evaluating children for apparently idiopathic epilepsy, even with onset in the first year of life and especially if additional features of CTX are present.

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Synopsis

CTX can present with infantile spasm, developmental delay, and cognitive decline in childhood.

Conflicts of Interest

AL, JDW-A, and TAB declare no conflicts of interest. PEB is a paid consultant to Retrophin, Inc.

Author Contributions

AL, JDW-A, and TAB: patient clinical evaluation, conception and design, and analysis and interpretation of data. AL and PEB: conception and design, drafting the article, and revising it critically for important intellectual content.

Compliance with Ethics Guidelines

All testing for this patient was performed as standard clinical care and thus was not considered human subject research.

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