Cerebrotendinous Xanthomatosis

George Anadiotis D.O.
Medical Director
Clinical and Biochemical Genetics
Randall Children’s Hospital
Case 1

- A 9 year old girl presents after the mother reads the ophthalmologist's chart and sees the diagnosis code, “disorder of aromatic amino acids”. It's the first time she's heard of this diagnosis and the doctor tells her not to worry about it too much after she brings it up. After looking this up on the internet she self-refers to genetics.

- Her daughter had been seen at that office since 1 year of age when it was noticed that the pupils were irregular.

- Physical exam was normal.

- The only other issue was that the child was on an IEP at school with an IQ in the low to mid 70's.
Problem 1
- Ocular albinism + iris irregularity + learning disorder = ?
- Ocular albinism + iris irregularity + learning disorder = ?

Foveal hypoplasia + aniridia + learning disorder = PAX6 gene
CTX is rare and underdiagnosed

Prevalence of CTX

- Approximately 425 cases of CTX have been reported worldwide
- Estimates of the prevalence of CTX in the general population range from 1 in 70,000 to 1 in 20,000
  > Based on these numbers, there may be as many as 4,500 to 15,900 individuals with CTX in the United States (population: ~318 million)
- CTX is much more frequent in certain genetically isolated populations, including Sephardic Jews (especially those of North African origin) and the Druze community
- In people of Moroccan Jewish ancestry, the frequency of the CTX gene has been estimated at 1/108, with a disease frequency of approximately 6/70,000

Challenges with diagnosing CTX

- Hallmark manifestations have variable onset and severity, which leads to delayed diagnosis and underdiagnosis
CTX is an autosomal recessive disease caused by mutations in *CYP27A1*

- CTX is inherited in an autosomal recessive pattern
- CTX is caused by mutations in the *CYP27A1* gene on chromosome 2q, which codes for the mitochondrial enzyme 27-hydroxylase
  > 27-hydroxylase catalyzes the first step in the acidic pathway for cholesterol elimination via conversion to bile acids in the liver
  > Sterol 27-hydroxylase deficiency reduces the production of bile acid
  > This leads to the accumulation of cholestanol in many tissues including the eye and brain
- 49 separate mutations in the *CYP27A1* gene have been identified in families with CTX
- No genotype-phenotype correlation has been observed in CTX
  Manifestations vary even in patients with the same mutations
AcetylCoA \rightarrow \text{HMG CoA} \rightarrow \text{Mevalonate} \rightarrow \text{Farnesyl-PP} \rightarrow \text{Squalene} \rightarrow 7\text{-Dehydrocholesterol} \rightarrow \text{Cholesterol}

1. Mevalonic aciduria/HIDS
   \text{↑ plasma & urinary mevalonate (↓ isoprenoids)}

2. Sjögren-Larsson Syndrome (SLS)
   \text{↑ Farnesylglucuronide ↓ Farnesolic acid}

3. Smith-Lemli-Opitz Syndrome (SLOS)
   \text{↑ 7-dehydrocholesterol ↑ isoprenoids, ↓ cholesterol}

4. Sitosterolemia
   \text{↑ sitosterol, ↑ cholesterol}

5. Niemann Pick Type C
   \text{↑ lysosomal cholesterol}

6. Cerebrotendinous Xanthomatosis (CTX)
   \text{↑ plasma cholesterol ↑ urinary bile alcohols}
Infant-onset chronic diarrhea

- **Prevalence**: In a systematic review of selected case series, the prevalence of chronic diarrhea in CTX patients was 48%.
- **Onset**: For many patients, diarrhea is the earliest symptom.
  - Diarrhea is usually described as being of childhood or infant onset, but may persist into adulthood in undiagnosed patients.
- **Mechanism**: The cause of diarrhea in CTX is not clear.
  - It is thought that elevated levels of bile alcohols may influence gut motility, affect fluid and electrolyte transport, or affect bacterial equilibrium.
Chronic diarrhea supports other hallmark manifestations in the diagnosis of CTX

- Patients and their caregivers often seek specialist advice for chronic diarrhea prior to diagnosis
  - However, there are many potential causes of chronic diarrhea in children and infants

<table>
<thead>
<tr>
<th>Possible causes of pediatric chronic diarrhea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With failure to thrive</strong></td>
<td><strong>Without failure to thrive</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic enteropathy</td>
<td>Chronic nonspecific diarrhea</td>
</tr>
<tr>
<td>Intractable diarrhea of infancy</td>
<td>Infectious colitis</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Lactose malabsorption</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Small bowel bacterial overgrowth</td>
</tr>
<tr>
<td>Immunodeficiency state</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td></td>
</tr>
</tbody>
</table>
Bilateral cataracts with juvenile onset

- Mean age of diagnosis - 35.5

- Birth
- Age 10
- Age 20
- Age 30

Prevalence: In a systematic review of selected case series, the prevalence of cataracts in CTX patients was 88%

Onset:
- Often present between the ages of 4 and 18 years
- Usually develop in the first 3 decades of life
- A smaller number of patients develop cataracts after neurologic symptoms are already advanced

Mechanism: Caused by buildup of cholestanol in the lens
- Vacuoles may form in the lens of affected patients
- CTX may disrupt the blood-aqueous barrier
Causes of bilateral cataracts with juvenile onset

- Causes of bilateral cataracts with juvenile onset include
  - Galactosemia
  - Diabetes
  - Uveitis associated with chronic juvenile arthritis
  - History of chronic corticosteroid use or whole body irradiation
  - Hypoglycemia or hypocalcemia

- Among patients with a known neurologic disorder presenting with early-onset cataracts, CTX may be the second most common cause after myotonic dystrophy.

*Unexplained bilateral juvenile onset cataracts are one of the hallmark manifestations and represent a key opportunity to diagnose CTX.*
Other ocular manifestations

In patients who have had CTX for many years (mean age = 44, range 32-54 years), the associated metabolic changes may lead to other ocular signs and symptoms

- **Optic disc paleness**
  - Dotti et al noted optic disk paleness in 6 of 13 CTX patients examined and Cruysberg et al also noted this finding

- **Optic neuropathy**
  - Increased visual evoked potential (VEP) latencies were observed in 11 of 12 patients in the Dotti case review
  - The authors theorized that high cholestanol concentrations could have led to abnormal myelination

- **Retinal vessel sclerosis**
  - CTX is associated with premature atherosclerosis and evidence of this may also be seen in the blood vessels of the retina
  - Retinal vessel sclerosis was seen in 4 of 13 patients in the Dotti study
Neurologic manifestations of CTX

- **Prevalence:** At the time of diagnosis (mean age: 35.5 years ± 11.8), approximately 60% to 70% of patients had pyramidal and cerebellar signs
  - Intellectual disability was apparent in well over 50% of patients at diagnosis
- **Onset:** Early signs of intellectual disability usually present when patients are of school age
  - Intellectual disability may progress to dementia when patients are in their twenties and thirties
  - Cerebellar and pyramidal neurologic signs also often develop in the third decade of life
- **Mechanism:** Patients with advanced CTX show evidence of lipid deposits and loss of white matter in many areas of the brain
Early neurologic manifestations

- Early developmental milestones may be achieved punctually, but patients then begin to fall behind.
- Patients may exhibit poor school performance, learning difficulties, sustained infantile behavior, and lack of age-appropriate self-care skills.

> "His problems dated to primary school. He had significant behavioral problems requiring a child psychologist’s input. He needed special help at school and has been very disruptive in class”

From a UK CTX case

- Epilepsy was present in 24% to 33% of patients at the time of diagnosis, with variable age of onset.
  > Some cases describe febrile seizures that persist beyond infancy into childhood.

- Early neurological signs of CTX may be subtle and can be mistaken for learning disorders, behavioral difficulties, ADHD and autism spectrum disorders.
Late neurologic manifestations

- In advanced cases, intellectual disability may progress to cortical/subcortical dementia from the third decade of life onwards.
- Parkinsonism is a rarer late manifestation of CTX that may occur in approximately 10% of patients.
- In a case review of 425 published cases of CTX, the incidence of psychiatric disturbances was 13%.
- Physically disabling neurologic dysfunction develops and progresses with increasing age in a majority of patients with CTX.
  - This includes pyramidal paresis, cerebellar ataxia, and peripheral neuropathy.
  - Spastic paraparesis and ataxia occurred in 77% and 62% of cases, respectively, usually at the end of the third decade.

- Patients with CTX whose diagnosis is missed or delayed may face severe intellectual and physical disability in their early adult years.
Mechanisms of neurologic deterioration in CTX

- Patients with advanced CTX show evidence of brain atrophy and lipid deposits in many areas of the brain
  > The white matter of the cerebellum, optic pathways, and pyramidal tracts are particularly affected

- Cholestanol accumulation in the brain of CTX patients may be caused by disruption of the blood-brain barrier, allowing lipids to pass more easily into the CNS
  > Patients with CTX had increased levels of albumin, apolipoproteins, and lecithin in their cerebrospinal fluid, in particular apolipoprotein B
  > Apolipoprotein B transports cholesterol into cells, and is typically present in very low levels in the CSF, likely due to its high molecular weight
Late neurologic manifestations

- In advanced cases, intellectual disability may progress to cortical/subcortical dementia from the third decade of life onwards.
- Parkinsonism is a rarer late manifestation of CTX that may occur in approximately 10% of patients.
- In a case review of 425 published cases of CTX, the incidence of psychiatric disturbances was 13%.
- Physically disabling neurologic dysfunction develops and progresses with increasing age in a majority of patients with CTX:
  - This includes pyramidal paresis, cerebellar ataxia, and peripheral neuropathy.
  - Spastic paraparesis and ataxia occurred in 77% and 62% of cases, respectively, usually at the end of the third decade.

- Patients with CTX whose diagnosis is missed may face severe intellectual and physical disability in their early adult years.
Tendon xanthomas in CTX

- Birth
- Age 10
- Age 20
- Age 30

Prevalence: In a systematic review of selected case series, the prevalence of tendon xanthomas in CTX patients was 69%

Onset:
> Often presents in the second or third decade of a CTX patient’s life

Mechanism: Caused by a buildup of cholestanol in the tendon(s)
> Foamy macrophages containing cholestanol, cholesterol, and other lipids infiltrate the tendon, disrupting collagen fibers in the connective tissue
> Can manifest as yellowish papules, plaques, nodules, and pseudotumors
> Most often affects the Achilles tendons

Mean age of diagnosis - 35.5

Tendon xanthomas
Differential diagnosis of tendon xanthomas

- Tendon xanthomas are unusual and warrant further investigation.
- They are associated with lipid disorders, including sitosterolemia, hyperlipoproteinemia, and familial hypercholesterolemia.
  - Sitosterolemia and familial hypercholesterolemia are associated with high plasma lipid levels.
  - Plasma cholesterol and lipid levels in CTX are usually normal or near normal.
  - Biochemical analysis of tendon xanthomas in patients with CTX characteristically shows high amounts of cholestanol and little cholesterol.

- CTX should be part of the differential in all patients with tendon xanthomas with normal serum triglycerides and cholesterol.
Other signs and symptoms of CTX

- Extensive osteoporosis, particularly involving the vertebrae and long bones of the upper and lower extremities
  - Early osteoporosis may occur in up to 67% of CTX patients but is typically subclinical, and only detectable by bone densiometry
  - 27-hydroxylase is also involved in vitamin D metabolism, which represents a possible mechanism for osteoporosis in CTX
- Atherosclerosis resulting in premature coronary heart disease and sudden death
  - A review of 144 cases noted that 10% of patients had cardiovascular disease
  - Cholesterol and cholestanol may also accumulate in the muscle of the heart, which may potentially affect atrial conduction and cause arrhythmia

- The diverse systemic effects of CTX lead to early development of osteoporosis and atherosclerosis commonly associated with advanced age
The primary biochemical test used to diagnose CTX is a blood test for cholestanol

- Currently, there are three specialty labs in the US that perform cholestanol tests, Oregon Health Sciences University (OHSU) in Portland, OR, the Kennedy Krieger Institute in Baltimore, MD, and Emory University in Atlanta, GA.

- Plasma cholestanol levels ≥5-10 times normal are highly specific for CTX and should be referred to a clinical geneticist/metabolic specialist.

- Genetic sequencing may also be used:
  - May choose a duplication/deletion and/or sequence analysis that specifically targets the CYP27A1 gene or a panel that tests for a variety of metabolic or mitochondrial disorders.
    - Although 49 separate mutations in the CYP27A1 gene have been identified in families with CTX, no genotype-phenotype correlation has been observed in CTX families, and symptoms vary even in patients with the same mutation.
Treatment

- Standard treatment involves the use of Chenodeoxycholic acid (CDCA) which inhibits excessive cholesterol and cholestanol synthesis.

- CDCA normalizes values and improves neurophysiologic findings, such as normalization of nerve conduction velocities, motor and sensory evoked potentials and stabilizes clinical manifestations.

- There also seems to be improvement in other neurologic manifestations such as psychiatric disease. However, once significant neurologic injury has occurred, effectiveness of treatment is limited.

- Age plays a very important role! Early treatment = better outcomes! There are some individuals who started treatment at an advanced age (>25 years) in which deterioration continued despite CDCA treatment.
Diagnostic pathway

Case of unexplained bilateral juvenile cataracts.

One or more hallmark manifestations may be present

Cholestanol blood test

referral to genetics

something weird
referral to genetics
YOU to patient: You don’t happen to have any other issues, like diarrhea or bumps on your tendons?

Patient (or patient’s parent): It’s interesting you ask. As a matter of fact I do!

YOU: Those things can be linked together. I’m going to send you on to this brilliant and handsome specialist.

Patient: I have never before received such excellent care! You are the best doctor ever!
YOU to patient: You don’t happen to have any other issues, like diarrhea or bumps on your tendons?

Patient or patient parent: No that’s not an issue

YOU: Well, thank God! because our toilet is broken and that would have been a disaster!

Patient: Thank you for this care! How is there not a statue in your honor?
Summary

- Cerebrotendinous xanthomatosis (CTX) is a rare and underdiagnosed, autosomal-recessive, metabolic disease
  - CTX is characterized by a bile acid deficiency which leads to a buildup of cholestanol throughout the body’s tissues
- CTX causes a distinctive array of hallmark manifestations
  - Infant-onset chronic diarrhea
  - Juvenile-onset bilateral cataracts
  - Tendon xanthomas
  - Progressive neurological deterioration
- CTX may be identified via a blood test for cholestanol
- If CTX is identified or suspected, refer patients to a clinical geneticist/metabolic specialist as soon as possible