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A Review on Cerebrotendinous Xanthomatosis (CTX): A Rare Autosomal Recessive Inherited Disease

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ABSTRACT

Cerebrotendinous Xanthomatosis (CTX) is a rare autosomal recessive disease which is caused due to the mutation of CYP27A1 gene that encodes sterol 27-hydroxylase enzyme. Due to the pathogenic variation in this enzyme the bile acid synthesis pathway gets disturbed which results in the production of bile acid intermediates especially cholesterol & bile alcohols and these gets accumulated in various parts of the body resulting in formation of xanthomas. There is no permanent cure for CTX but the early detection and treatment with cholic and chenodexycholic acids have proven to reduce the severity of the condition. CTX is a genetic disease which generally prevails from the early childhood and lasts throughout the life. Thus, proper genetic counseling is recommended to help families understand the genetics and natural history of CTX, and also to provide the psychosocial support.

Introduction

Cerebrotendinous Xanthomatosis (CTX) also called as Cerebral Cholesterosis, is a rare inborn error of bile acid metabolism due to the homozygous mutation of the hepatic mitochondrial enzyme 27-sterol hydroxylase (CYP 27) which makes it an autosomal recessive inherited disease. In general, CTX is a lipid storage disorder associated with the deposition of a steroid known as cholestanol in the brain and other tissues. It is mainly characterized by elevated levels of cholesterol in plasma but with normal total cholesterol levels, progressive cerebellar ataxia (beginning of puberty), juvenile cataracts, juvenile or infant onset chronic diarrhea, childhood neurological deficit, tendineous or tuberous xanthomas, osteoporosis, coronary heart disease and progressive neuropsychiatric disturbances. CTX is associated with considerable variability in clinical manifestations among patients and even within same family.

CTX is a rare disease which has been observed more among the females than in males. Mainly the treatment option for this condition is replacement with chenodeoxycholic acid (CDCA) in the early stages of the disease and it has been reported to be an effective way to improve or prevent the clinical symptoms of CTX. In this article, we mainly reviewed the current underlying pathogenesis, clinical manifestations, diagnosis and management of CTX [1,2].

Pathophysiology

The *CYP27A1* gene encoding sterol *27-hydroxylase* is the key enzyme in the bile acid synthesis pathway, and mutation of this gene results in CTX. The classical bile acid synthesis pathway is initiated by *7alpha-hydroxylation* of cholesterol and is catalyzed by the rate limiting enzyme cholesterol *7alpha-hydroxylase*. Also, there is an alternative pathway which is initiated by *27-hydroxylation* of cholesterol which is done by *sterol 27-hydroxylase*. This sterol *27-hydroxylase* enzyme facilitates the removal of cholesterol from the body through its conversion into bile acids i.e chenodeoxycholic and cholic acid.

In patients with CTX, pathogenic variation of the gene results in lack of sterol *27-hydroxylase* enzyme due to which the bile acid pathway intermediates remains unused along with components like cholestanol and bile alcohols. The negative feedback effect of CDCA on cholesterol *7alpha-hydroxylase* is inhibited and thus it accelerates these metabolic

abnormalities, leading to increased levels of bile acid intermediate *7alpha-hydroxy-4-cholesterol-3-one* as a precursor for cholestanol and bile.

CTX is inherited in an autosomal recessive pattern, so a child must inherit a pathogenic variance in the *CYP27A1* gene from both parents who are carriers in order to be affected. Parents who are carriers have one normal *CYP27A1* gene and one pathogenic *CYP27A1* gene variant and have a 25% chance to have an infected child with another carrier regardless of whether the child is male or female [3].

Clinical Manifestations

Clinical presentation of CTX is characterized by diverse systemic and neuropsychiatric manifestations and combinations of symptoms vary from patient to patient. Systemic symptoms include neonatal jaundice or cholestasis, chronic diarrhea, juvenile cataracts, xanthomatosis, osteoporosis and coronary heart disease. These symptoms can range from mild to severe and can appear from infancy through adulthood. In infants the disease may first present as chronic diarrhea that remains unchanged despite treatment or seizures often called infantile spasms. Infants with CTX may develop cholestatic liver disease where bile can stagnate in the liver, causing symptoms such as jaundice and liver enlargement.

Children may develop juvenile cataracts that can manifest as difficulty following objects with the eyes, eyes pointing in different directions, or cloudiness over the eyes lens. Neurological symptoms can appear in childhood or later in life, and may include cognitive impairment, such as difficulty with memory, concentration and reasoning. Other symptoms may include epilepsy and spasticity, causing difficulties in movement and speech. Adolescence may display behavioral changes such as agitation, aggression and depression and may also experience hallucinations and suicidal thoughts. In early adulthood Tendinous Xanthomas may appear with fatty bumps or nodules formed around the elbows and knees and heels. If the disease remains untreated and continues to progress, affected individuals may become wheelchair-bound and continued neurological decline may lead to early dementia. CTX is also linked to atherosclerosis osteoporosis and hyperthyroidism which present as fatigue, sensitivity to cold, weight gain and thinning hair [4].

Diagnosis

Diagnosis begins with an assessment of the individual's medical history and includes genetic and biochemical testing for confirmation of disease. Genetic testing identifies pathogenic variation in *CYP27A1* gene and biochemical testing confirms a lack of *sterol 27-hydroxylase* activity. The biochemical testing typically presents normal to low blood cholesterol levels and little to no chenodeoxycholic acid and cholic acid. CTX is biochemically confirmed by the presence of high blood concentrations of cholestanol, bile acid pathway intermediates and bile alcohols. Bile alcohols are also present at high concentrations in the urine. Imaging tests may also be used to determine disease progression and can include CT or MRI of the brain.

Treatment

Treatment for CTX optimally requires early diagnosis and treatment to prevent the complications. Treatment at any stage can be helpful to stop disease progression, but it generally cannot reverse any existing neurological damage. Treatment involves oral bile acid replacement therapy. Chenodeoxycholic acid is the first line therapy as it helps normalize the levels of cholesterol, bile acid intermediates and bile alcohols. Cholic acid may also be considered for children as it can be less toxic for the liver than chenodeoxycholic acid. Genetic counseling is recommended to help families understand the genetics and natural history of CTX, and also to provide the psychosocial support [5].

Conclusion

CTX is an autosomal recessive inherited disease, which mainly occurs due to the deposition of cholestanol in brain and other tissues. Clinical symptoms could be seen since childhood, which makes it essential to diagnose at its early stage. Since permanent cure of this disease is still unknown, but early detection and use of Chenodeoxycholic acid and cholic acid can prevent it up to some extent.

Abbreviations

- CDCA - Chenodeoxycholic acid
- CTX – Cerebro Tendinous Xanthomatosis
- CT - Computed Tomography
- MRI - Magnetic Resonance Imaging

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