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Cerebrotendinous Xanthomatosis- A Case Report

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal-recessive lipid storage disease caused by mutations in the CYP27A1 gene; this gene codes for the mitochondrial enzyme sterol 27-hydroxylase, which is involved in bile acid synthesis. The CYP27A1 gene is located on chromosome 2q33-qter and contains nine exons. A CYP27A1 mutation leads to decreased synthesis of bile acid, excess production of cholestanol, and consequent accumulation of cholestanol in tissues. Currently there is no consensus on the prevalence of CTX, one estimate being <5/100,000 worldwide. Patients with CTX have an average age of 35 years at the time of diagnosis and a diagnostic delay of 16 years.

KEYWORDS

Cerebrotendinous xanthomatosis, Xanthoma, CYP27A1, Sterol 27-hydroxylase, Chenodeoxycholic acid and Cholic acid.

INTRODUCTION

Cerebrotendinous xanthomatosis is a rare autosomal recessive form of xanthomatosis and falls within a group of genetic disorders called the leukodystrophies. Approximately 425 cases have been reported worldwide. Prevalence- 0.13 in 1,00,000 population.

Primary enzyme defect is mitochondrial sterol 27 alpha hydroxylase which is a key enzyme in the complicated process of bile acid synthesis from cholesterol. Therefore bile acid precursors accumulate in tissues resulting in degenerative process.

CASE REPORT

A 20 Year Old Female admitted with history of swellings over posterior aspects of both ankles for the past 6 months and swelling over dorsal aspect of left hand for the past 2 months insidious, progressive, painless, nodular and mobile swellings. She had history of chronic diarrhoea in childhood, Congenital cataract in both Eyes and surgery done at age of 7. She discontinued education due to poor scholastic performance. History of one episode of generalized tonic-clonic seizure at the age of 9.

GENERAL EXAMINATION

Patient was conscious, Oriented, Afebrile**,** Short Stature-142 Cm, Short Neck, Low Set Ears.

Vital signs**-**PR-74/min, BP-100/70mmhg, RR-12/min,SPO2-97% in room air.

Cardiovascular System- S1S2 present, no murmur.

Respiratory System-normal vesicular breath sounds present, no added sounds

Abdomen-Normal

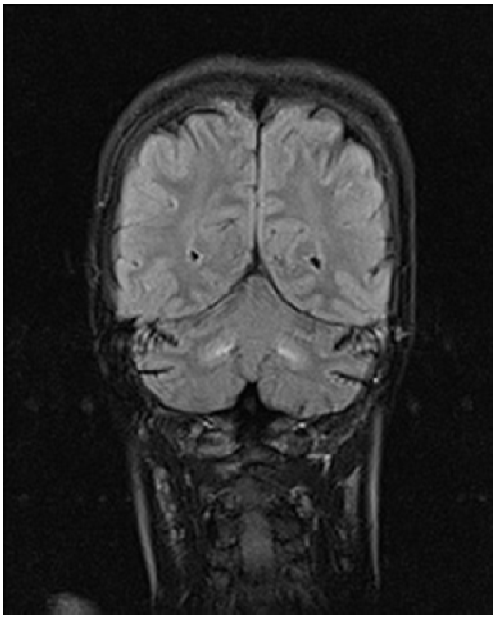
Central Nervous System

Intentional Tremors present in both hands. Inco-ordination in the form of Dysdiadokinesia, difficulty in Finger Nose Test, Heel Shin Test on Both Sides.

LOCAL EXAMINATION

Left ankle- swelling of size 5x4 Cm over achilles tendon, Nodular, Smooth Surface, Firm, Mobile, Non-Tender Right Ankle- swelling of Size 6x2cm, Nodular, Smooth Surface, Firm, Mobile, Non-Tender. Left wrist-swelling of size 2x2 Cm dorsal aspect, Firm, Mobile, non-Tender.

TENDINOUS SWELLING IN RIGHT ANKLE



DENTATE NULCEUS HYPERINTENSITIES

INVESTIGATIONS

Hb-11.3 g/dl, Total count- 7900 per microliter, Platelet-2,32,000 per microliter

Sugar-103 mg/dl, urea-23 mg/dl, creatinine-0.8 mg/dl, serum sodium-136 mEq/L, serum potassium-3.7 mEq/L.

Serum bilirubin-1.2 mg/dl, direct-0.3 mg/dl, indirect-0.9 mg/dl, total protein- 6.5 g/dl, albumin-4 g/dl, globulin-2.5 g/dl, SGOT-23 IU/L, SGPT-20 IU/L, ALP-56 IU/L.

Serum Total Cholesterol-193 mg/dl, Serum Hdl-63 mg/dl, Serum Ldl -94 mg/dl, Serum Triglycerides-173 mg/dl, Serum Cholestanol-147 Micromol/L(10 To 12)

ECG-Normal, Chest X-Ray –Normal, X-Ray Left Wrist and Both Lower Limbs – Normal, USG Abdomen And Pelvis- normal.

FNAC RIGHT AND LEFT TENDOACHILLIS SWELLING

Multi-Nucleated Giant Cells having foamy cytoplasm along with many singly scattered foamy Histiocytes In a background of Red Blood Cells. Features suggestive of Tendinous Xanthomatosis.

MRI BRAIN WITH MRA AND MRV

Bilateral Dentate Nuclei show T2/Flair Hyperintense Signals (CT Screening Reveals No Significant Calcification). With history of Tendon Xanthomas and Congenital Cataract, MRI features are consistent with Cerebrotendinous Xanthomatosis.

DISCUSSION

Our patient is a rare case of Cerebrotendinous xanthomatosis. Clinical signs and symptoms of cerebrotendinous xanthomatosis include adult-onset progressive neurological dysfunction (i.e., ataxia, dystonia, dementia, epilepsy, psychiatric disorders, peripheral neuropathy, and myopathy) and premature non-neurologic manifestations (i.e., tendon xanthomas, childhood-onset cataracts, infantile-onset diarrhea, premature atherosclerosis, osteoporosis and respiratory insufficiency). Juvenile cataracts, progressive neurologic dysfunction, and mild pulmonary insufficiency are unique symptoms that distinguish CTX from other lipid storage disorders including familial dysbetalipoproteinemia, homozygous familial hypercholesterolemia, and sitosterolemia, all of which might also present with xanthomas and cardiovascular diseases. Brain magnetic resonance imaging (MRI) shows bilateral lesions in the dentate nucleus of the cerebellum and mild white matter lesions. The classical symptoms and signs, namely elevated levels of cholestanol and bile alcohols in serum and urine, brain MRI, and the mutation in the CYP27A1 gene confirm the diagnosis of CTX.

Monitoring plasma cholestanol levels can be used to assess the biochemical effects of CDCA and cholic acid in patients with CTX before and after treatment. However, serum cholestanol level has no correlation with clinical features. A possible explanation is that increased cholestanol level is not the only factor important for pathogenesis in CTX. Further studies are required to understand any other underlying mechanisms and to provide reasonable explanations. Moreover, further studies are needed to discover why some patients with CTX develop White Matter lesions in the brain.

CONCLUSION

CTX is an inherited lipid metabolic disorder with diverse manifestations. The classical symptoms and signs, namely elevated levels of cholestanol and bile alcohols in serum and urine, cranial magnetic resonance imaging, and mutation in the CYP27A1 gene, confirm the diagnosis. Patients with CTX have an average diagnosed age of 35 years and a diagnostic delay of 16 years. Early diagnosis and long-term treatment with CDCA (750 mg/d) can improve neurological symptoms and contribute to a better prognosis.

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