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Case Report

A case report on cerebrotendinous xanthomatosis

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a rare hereditary neuro-metabolic disease in which deposition of cholesterol and cholestanol occurs in various tissues including CNS. It is characterized by juvenile cataract, tendon xanthomas and progressive neurological defects. It is one of a group of neurologic disorder collectively referred to as leukodystrophy, which predominantly affects the CNS white matter. We are presenting a patient with cerebrotendinous xanthomatosis, who is now 36 years old, and shows the natural course of disease in an untreated patient. He presented with xanthomas on Achilles tendon, elbow and knees and showed cerebellar and pyramidal signs. He had recurrent seizures and was mentally subnormal.

Keywords: Cerebrotendinous xanthomatosis, Tendon xanthoma, Cholestanol lipidosis, Chenodeoxycholic acid

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) or cholestanol lipodosis is a treatable genetic lipid metabolic neuro degenerative disorder.[1] Xanthomatosis refers to the formation of fatty yellow nodules (xanthomas). Cerebrotendinous refers to the typical locations of the xanthomas (cerebro-meaning the brain and tendinous meaning connective tissue called tendons that attach muscle to bone).[2] The principal manifestations of CTX are juvenile cataract, tendon xanthoma and neurological symptoms.[3] A review of literature revealed 175 patients with documented CTX of which 56% were female, 71% had tendon xanthoma, 81% had low intelligence and incidence of cataract and other neurological symptoms were seen in 92% cases.[4] A deficiency of the enzyme sterol-27-hydroxylase causes accumulation of cholesterol and cholestenol in virtually all tissues. Fat deposition leads to formation of xanthomas, nodules and plaques in CNS, tendon, skin, lungs and bones.[2] It is caused by defects in synthesis or maintenance of myelin sheath that insulates nerves. While there is no cure for disease, its early diagnosis and treatment with chenodeoxycholic acid (CDCA) can alter the course of disease.[5,2]

CASE REPORT

A 36 year old man was admitted in the neurology department of a tertiary care teaching hospital. He presented with complaints of difficulty in speaking& food intake for past 3 years. He had recurrent episodes of aspiration pneumonia.

Past history of patient suggestive of CTX

The patient was the second child of a non-consanguineous marriage. The child was born at home without medical assistance. Delayed onset of crying was noted at the time of birth. He had apparently normal growth until 9 months of age, when he developed seizures (GTCS) and was started on phenytoin and phenobarbitone. Since 9 months motor and social mile stones were delayed. He started walking at the age of 2 years, sent to school and studied up to 4th standard but

discontinued due to poor scholastic performance. He developed jaundice at the age of 12. Deterioration of motor skills started at around 14 years of age. By 15 years of age he noticed swelling over Achilles tendon, knees and elbow which were firm in consistency. Fine needle aspiration cytology (FNAC) was done and the swelling was suggestive of xanthoma containing foam cells and macrophages. The laboratory investigation showed normal lipid profile. The MRI of patient suggested high signal intensity along pyramidal tract, dentate nuclei, deep cerebellar white matter and globus pallidus (Figure 1). These findings were consistent with features of CTX. The patient was advised to take chenodeoxycholic acid (CDCA), but due to its unavailability and lack of financial support they were unable to treat with the same. He had recurrent episodes of seizures during these periods and was on antiepileptic (Phenytoin 100 mg 1-0-2, Phenobarbitone 60 mg 1-0-2).

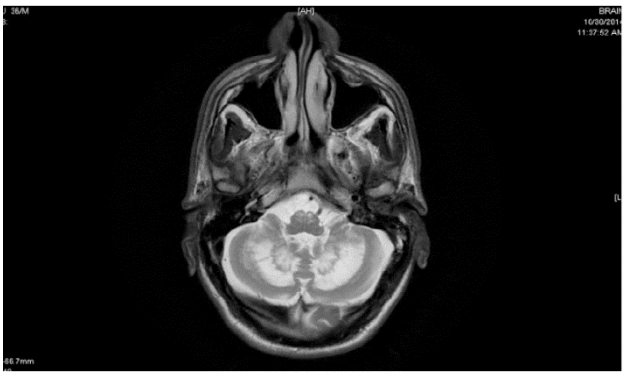

Figure 1: MRI: T2 weighted image showing bilateral cerebellar hyperintensities with typical changes in dentate nucleus.

By 30 years of age he developed increased aggressiveness and was prescribed with antipsychotic medication. On examination bilateral pyramidal signs (increased jaw jerk, disuse atrophy of all muscles of both upper and lower limbs, brisk deep tendon reflexes and clonus), cerebellar signs (ataxia and nystagmus) and extrapyramidal signs were noted. He was prescribed with benzhexol, baclofen and vitamin tablets. The patient started to have difficulty in walking - initially as heaviness of both legs with difficulty in walking over irregular surfaces. Soon he developed slurring of speech, difficulty in seeing far objects and bilateral immature cataract. The weakness of legs progressed and patient became chair bound. The seizures which started as GTCS progressed to multiple seizure types (complex partial, simple partial and myoclonic jerks) which were found to be drug resistant. There was a steady decline of cognitive function and intellectual abilities. The patient was bed ridden for past 1 year and had decreased sleep and minimal talk. For the past 3 years he had difficulty in swallowing, intermittent fever and recurrent aspiration. He was admitted for the same. He was still on antiepileptic and antipsychotic medications. Long term therapy with phenytoin resulted in osteoporosis of skull.

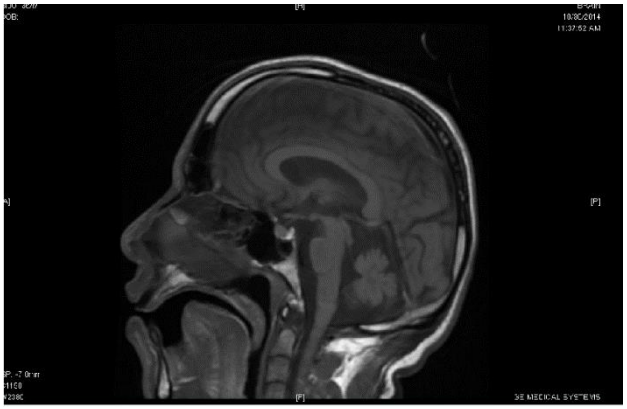

Figure 2: MRI: T1 weighted sagittal image showing cerebellar atrophy.

He had recurrent episodes of aspiration which lead to pulmonary insufficiency that progressed to aspiration pneumonia. Clinical evaluation revealed psychomotor retardation, bilateral contractures and multiple tendon xanthomas. EEG showed bitemporal & temporooccipital epileptiform activities. MRI revealed bilateral symmetric T2 flair hyperintensities in brain parenchyma with mild premature atrophy (Figure 2). His lipid profiles were normal. He developed high grade fever after admission and treated symptomatically with IV antibiotics, and then he was discharged.

DISSCUSION

Cerebrotendinous xanthomatosisis a rare genetic lipid metabolic disorder of cholesterol and bile acid metabolism in which the deposition of a form of cholesterol (Cholestanol) in the brain and other tissues occur.[5] The disease was first described in 1937 by Van Bogaert.[6] More than 300 patients have been diagnosed worldwide. CTX is very rare in Indian population. In 1999 Gobinda et al reported CTX in 2 siblings from Indian family.[4] CTX can occur at any age from the neonatal period to the sixth decade of age or later and is not associated with anysex predilection.[7]

It is an autosomal recessive disorder associated with mutations in CYP 27A1 gene located on chromosome 2q33-qter (autosome) which codes for enzyme sterol-27 hydroxylase.[8,9] This is a key enzyme in the complicated process of bile acid synthesis from cholesterol. Defects in the enzyme result in decreased synthesis of bile acid, chenodeoxycholic acid (CDCA). This in turn disrupts feedback regulation of cholesterol 7 alpha- hydroxylase which is the rate limiting step in the bile acid synthesis. Therefore bile acid precursor cholesterol accumulates in tissues.[1,2,5,6,10]. Deposition of cholestanol and cholesterol in CNS (brain and spinal cord), muscle (including heart muscles),blood vessels, eye and tendon result in a degenerative process that worsen over time unless treated.[11] Xanthomas can also accumulate in the fatty substance that insulates and protects nerves (myelin), disrupting nerve signaling in the brain. Disorders that

involve the destruction of myelin are known as leukodystrophies. Patient with CTX appear to have a diffuse decrease in total brain volume. The decrease being predominantly in cortical grey matter rather than white matter.[2,7]

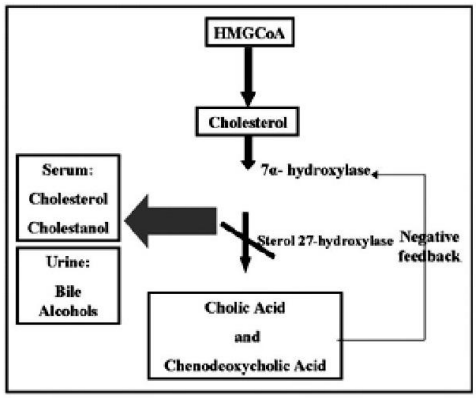

Figure 3: Bile acid synthesis.[1,12]

This lipid storage disease is characterized by infantile onset diarrhoea, childhood onset cataract that is in 1st decade, adolescent to young adult onset tendon xanthomas (soft humps under the skin made up of yellow fatty deposits) which occurs in 2nd 3rd decade and adult onset progressive neurological dysfunction (dementia, psychiatric dysfunctions, pyramidal/ cerebellar signs, dystonia, atypical parkinsonism, peripheral neuropathy and seizures by 3rd decade.[3,5,8] Xanthomas may occur on the Achilles tendon, extensor tendon of elbow and hand, patellar tendon, neck tendon, lung, bones & nervous system. Neonatal or infantile hepatitis, prolonged jaundice, premature atherosclerosis and osteoporosis are also common in this disease.[3,5,8,12]

Early diagnosis is extremely important as patient benefit from therapy and prevents brain damage that can lead to severe mental dysfunction and eventually death.[8] Diagnosis includes:

1. Clinical diagnosis[3]
2. Biochemical testing: high plasma cholestanol concentration, normal to low plasma cholesterol concentration (lipid profile), markedly decreased formation of CDCA, increased concentration of bile alcohol and their glyconjugates in bile, urine and plasma, increased concentration of cholestanol and apolipoprotein B in CSF resulting from changes in BBB &cholestanol–cholesterol ratio.[3,4]
3. MRI studies: Conventional MRI imaging have shown diffuse and focal abnormalities of the white matter, cerebral and cerebellar atrophy and a typical abnormal MR signal intensity change of the dentate nuclei and the surrounding white matter.[1,3,4,9]
4. Biopsy of tendon xanthoma or subcutaneous swellings. It reveals foam cells and touton giant cells. Spindle-shaped clefts are seen in the xanthomas on hematoxylin and eosin staining and rod shaped collections are seen on electron microscope.[5]

Cataract, progressive neurological symptoms and pulmonary insufficiency are unique features that distinguish CTX from familial hypercholesterolemia and sitosterolemia.[3,5,12]

The primary and effective treatment for CTX is chenodeoxycholic acid replacement therapy. CDCA has been found to normalize bile acid metabolisms and to slow, halt and even reverse problems of CTX. Typical adult dose is 750 mg/day or 50 mg/kg/day orally 3 times a day.[3,4,11] It is a very costly medicine and it's not available in India.[1] The major side effects of CDCA may be diarrhoea, restlessness and impatience.[12] If hypercholesterolemia is not controlled with CDCA treatment alone, HMG-CoA reductase (Simvastatin and Pravastatin) may be added.[3] Low density lipoproteins apheresis can also be indicated. Cholic acid is alternate to CDCA with decreased hepatotoxicity has been used to treat children with CTX. Surgical excision of bilateral tendon may worsen the gait imbalance and cannot prevent the deterioration of neurologically affected patients.[5,12] Due to the diverse manifestations and signs of CTX, symptomatic therapy is essential: antidepressant medication in case of depression, antiepileptic therapy in case of convulsive seizures, levodopa in case of Parkinsonism, and botulinum toxin in case of dystonia.[5]

In our case the patient's clinical symptoms and MRI report suggested of CTX. Genetic mutation analysis of his parents was not carried out. The cholestanol level values were unavailable. He was treated symptomatically and discharged. Patient surviving for 36 yrs. without specific treatment is very rare.

CONCLUSION

Cerebrotendinous xanthomatosis is a familial disorder of bile acid synthesis. Early detection and treatment of CTX significantly reduces the complications of the disease. The diagnosis of CTX should be suspected and ruled out in all cases of congenital or juvenile cataract, spastic diplegia, paraparesis, quadriparesis or ataxia or combinations of these features particularly on a background of chronic diarrhoea even in the absence of tendinous xanthomas, which often do not appear till 2nd decade of life. Raised plasma cholestanol levels are diagnostic of the disease early in course. Genetic testing in presymptomatic family members of affected patients should be done and CDCA therapy instituted to prevent the disease manifestations. Limitation of the study is that plasma cholestanol level and genetic studies were not performed.

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