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CerebroTendinousXanthomatosis-A Rare Clinical Entity-Case Report

Samrat Vishnu Vardhan T[1], Navaneetha S[2], Arun kumar B[2], Vijayalakshmi M[3], Shekar Y Tati[4],RavinderNathML[5], Mahendar Reddy G[6].

1. Asst. Professor2.Residents, 3.Associate Professor, 4. Consultant-Department of General Surgery.
5. Professor, 6. Associate Professor – Department of Radio Diagnostics
MediCiti Institute of Medical Sciences, Medchal, Hyderabad, Telangana, India.
Corresponding author: Samrat Vishnu Vardhan T[1]

Abstract: *Cerebro-tendinousxanthomatosis (CTX) is a genetic disorder of metabolic origin..It is an inborn error of bile acid metabolismtransmitted by an autosomal recessive gene characterised by juvenile cataract, tendon xanthomas and neurological symptoms due to degenerative changes in the cerebellum and cerebrum of the brain and xanthomas in the tendons.37 years old femalepresented with multiple swellings over both the tendons of Achilles, elbow and patellar tendon along with cerebellar and pyramidal signs. She had recurrent seizures and was mentally subnormal. She also had cataractin the right eye underwent surgery four years ago.*
X- Rays and MRI of the leg showed soft tissue masses on both Achillestendons and MRI Brain showed bilateral hyper intensive lesions in dentate nucleus of cerebellum. FNAC fromtendon swellings showed features of Xanthomas. Serum cholesterol was slightly elevated. The case was diagnosed as cerebrotendinousXanthomatosis(CTX) syndrome. Surgery is not indicated in Xanthomas as it is a degenerative diasease. Medical treatment is only the choice. Chenodeoxycholic Acid was started and patient is under follow up. We wish to report this case as it is a rare disease, only few hundred cases are reported in the literature and it is first case in our experience.

Keywords: *CerebrotendinousXanthomatosis (CTX), Chenodeoxycholic Acid (CDCA), Cholesterol, Cholestanol,Xanthoma*

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I. Introduction

Cerebrotendinousxanthomatosis (CTX) is a rare genetic metabolic disorder of cholesterol and bile acid metabolism resulting in systemic and neurologic abnormalities [1]. CTX was first reported by van Bogaert in 1937and it is also called as Van Bogaert–Scherer–Epstein syndrome. It is due to mutation of CYP27A1 gene located on chromosome 2q33-qter which codes for enzyme sterol 27-hydroxylase, involving in bile acid synthesis [2]. Mutation of this gene leads to decreased synthesis of bile acid, chenodeoxycholocacid (CDCA) resulting in disruption of feedback regulation of cholesterol 7 alpha –hydroxylate, limit the bile acid synthesis. Therefore bile acid precursor cholesterol accumulates in the tissues. [3,9].Cholesterol and cholestenol deposit in the brain, spinal cord, muscles and tendon, eyes and blood vessels[4].

CTX can occur at any age from neonatal to 6th decade however the average age of diagnosis is at 35 years. It presents as xanthomatosis of brainmanifesting with symptoms of dementia, seizures, intellectual disability and psychiatric disturbances. Tendinousxanthomas are hall mark of the disease particularly on tendo Achilles, patellar tendon and Elbows. Patient may also present with juvenile cataract, intractable diarrhoea in infants[5].

Laboratory studies: lipid profile reveals elevated plasma and serum cholestanol levels and low-to-normal cholesterol levels. The cholesterol-to-cholestanol ratio is said to be a better indicator of disease than cholestanol concentration alone [1].A low cholesterol-to-cholestanol ratio is diagnostic.

MRI images show cerebral and cerebellar atrophy along with atrophy of white matter. High signal intensity is seen along the (T2 hyperintensity) dentate nuclei, pyramidal tract, deeper cerebellar white matter is a characteristic feature of cerebrotendinousxanthomatosisand it is seen in 79% ofpatients[2,3].Bilateralbrain lesions consistent with a metabolic abnormality are a diagnostic featureof CTX. Plain lateral Radiographs and MRI picture shows soft tissue masses without any signs of calcifications.FNAC shows collection of foamy macrophages surrounded by foreign body type multinucleate giant cells further confirms the diagnosis. There is no role of surgery, early diagnosis and treatment with chenodeoxycholic acid can alter the course of the disease.

II. Case Report

A 37 years old lady presented with swellings over both the Achillestendons since 32 years which were gradually progressing. The size of the swellings was 20x6 cm, surface was lobulated (fig1),firm in consistency. The swelling was mobile horizontally withrestricted vertical mobility. Similar swellings were noted on the elbow, patellar tendon, and great toes. She developed seizures 5years back and underwent cataractsurgery in right eye 4years back. On examination patient was anaemic. serum cholesterol levels were slightly elevated, cholestanol levels were not estimated due to non availability. Plain radiographs of both Ankles showed soft tissue swellings over both thetendo-achilleswithout signs of calcifications. MRI Brain showed bilateral hyperintensity in dentate nucleus of cerebellum(fig2).FNAC showed foamy macrophages and giant cells(fig3).Genetic study was not carried out in our case. Chenodeoxycholic Acid was started, 15mg/kg body weight/day along withStatins.Patient is under follow up.

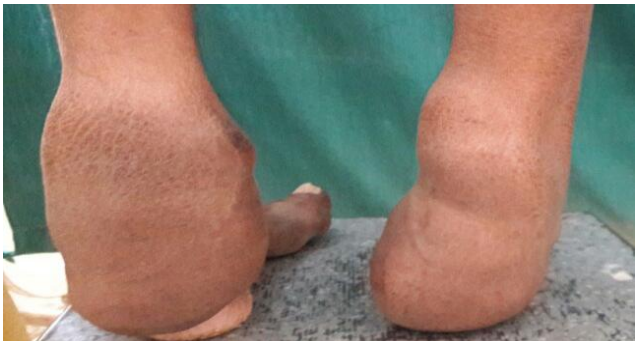

Figure 1.Showing tendinousxanthomas on both Achilles tendons.

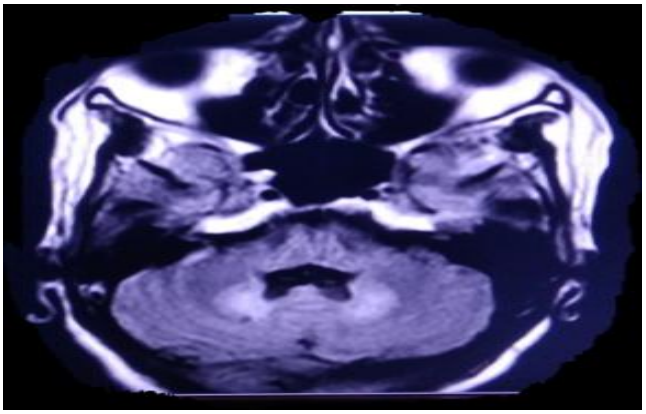

Figure 2. Axial sections of flair on MRI showing hyper intensity in dentate nuclei of cerebellum

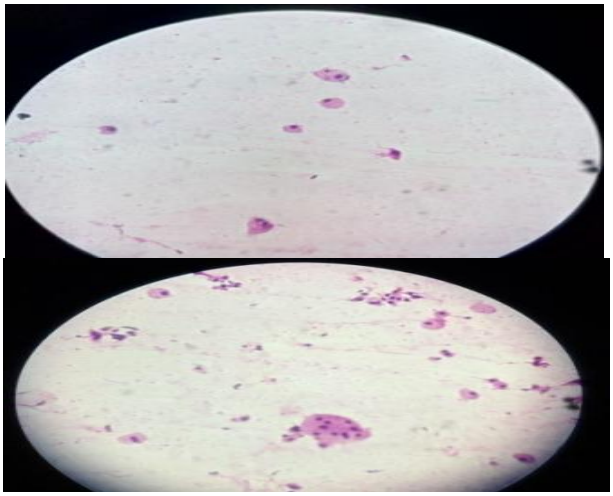

Figure 3. FNAC showing foamy macrophages and multi nucleated giant cells

III. Discussion

Cerebrotendinousxathomatosis (CTX) is a rare autosomal recessive genetic lipid metabolic disorder of bile acid metabolismIt is caused by genetic mutation of CYP27A1 gene located on chromosome 2q33-qter which codes for enzyme sterol 27-hydroxylase, which involve in bile acid synthesis [1,2,3]. Deficiency ofenzyme results in decreased synthesis of bile acids, chenodeoxy- cholic acid, thisinturn disrupts the feedback regulation on cholesterol 7-alpha-hydoxylase, limit the step in bile acid synthesis. Therefore bile acid precursors accumulate in the tissues [5].Deposition of cholestanol and cholesterol occur in the CNS, Muscle, blood vessels, eye and tendons resulting in a degenerative process that worsens over time unless treated otherwise[6].

It is a rare disease around 300 cases had been reported worldwide so far [7]. It is uncommon among the Indian population [8]. It is more common in females the reported female incidence in the literature is 56%, incidentally our patient is also a female. The disease prevalence is <5/100,000 [9]. The mean age for the presentation of symptoms is 19 years, however, mean age at the time of diagnosis is 35 years[10]. Our patient age was also 37 years indicating the diagnostic delay. CTX is characterised by deposition of cholestanol in the brain both in the cerebellum and cerebrum and in the tendonsresulting in tendon xanthomas more so on tendo-achilles, elbow and patellar tendon. In early infancy patient may have diarrhoea, may develop juvenile cataract. All the features were present in our case. In the world literature, thereported incidence of xanthomas are71%, decreased intelligence levels noted 81% and presence of neurological symptoms in 92% of the cases[8]. Tendon xanthomas usually start arising in the second decade of life.

Presence of any 2 out of 4 criteria i.e. cerebral tendon xanthomashyperintensity of dendatewith juvenile cataract, warrants testing for CTX. Biochemical testing shows high plasma cholestanol concentration with low to normal serum cholesterol levels. Cholesterol-to-Cholestanol ratio is said to be a better indicatorthancholestanol concentrationalone. There is increased concentration of bile alcohol and their glyconjugates in bile, urine and plasma[11, 12]. MRI brain show bilateral cerebellar atropy with typical abnormal signal intensity change in the dentate nuclei and surrounding white matter[11, 13]. FNA biopsy reveals foamy macrophages and giant cells with spindle shaped clefts are seen in the xanthomas[3].

No surgical treatment. Surgical excision of tendenousxanthomas pose problem in gait imbalance and cannot prevent degenerative changes [14]. The condition is treated by replacing the bile acids ,chenodeoxycholic acid (CDCA). It helps torelieve both neurological and non neurological symptoms [15]. symptoms are completely reversed when the condition is diagnosed and treated early. It is found to normalize bile acids metabolism and to slow down or reverse the symptoms of CTX. Adult dosage is 750mg/day or 50mg/kg body weight/day orally three times a day [4,8, 11,].The major side effects are diarrhoea, restlessness and impatience.

IV. Conclusion

Cerebrotendinousxanthomatosis is an inherited lipid storage disorder of bile acid synthesis. The gene CYP27A1 is responsible which located on chromosome 2q33-qter.The disease characterised by cerebral and tendinousxanthomatosis along with diarrhoea and juvenile cataract. It is more common in females, can present from infancy to middle age. The average age of diagnosis is 35 years, indicating delay in the diagnosis resulting in unsatisfactory treatment. Clinically patient presents with mass lesion on the tendoachilles and other tendons, patient may have juvenile cataract. The serum cholestanol levels are elevated with normal or low levels of cholesterol. The cholestanol/cholesterol ratio is better indicator to diagnosis. MRI brain confirms the cerebellar lesion and X- ray part reveal soft tissue masses on the tendoachilles. Early diagnosis and long term treatment with CDCA can improve neurological symptoms and will have better prognosis.

V. Prognosis

It is a progressive degenerative disease, ultimately involves the vascular component resulting atherosclerosis which leads to death.Delayed diagnosisand non availability and patient ability to purchase CDCA are main cause for prolonged morbidity. Life expectancy in CTX is hardly to extend beyond fifth and sixth decades of life.

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No conflict of interest

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