Rare disease

Cerebrotendinous xanthomatosis: a rare genetic disorder

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A 32-year-old male patient presented with uncontrolled convulsions to the emergency room. He had epilepsy since childhood and was on tablet phenytoin sodium 100 mg three times a day. However, on detailed history elicitation and clinical examination, he was found to have a constellation of findings. He had multiple swellings over both the lower limbs and upper limbs at the site of various tendon insertions (xanthomas), mental retardation, speech disturbance, bilateral pyramidal tract involvement and bilateral cataracts. Based on clinical features, a diagnosis of cerebrotendinous xanthomatosis: a relatively rare genetic disorder was suspected, and later on confirmed histopathologically.

BACKGROUND

Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid-storage disease caused by mutations in the sterol 27-hydroxylase gene. Deficiency of the enzyme 27-hydroxylase causes an impairment of the metabolic pathway of cholesterol, resulting in an excessive production of cholestanol, which then accumulates in many tissues.¹ Recognition of tendon xanthomas in a young patient with neurologic symptoms like epilepsy, spastic paraparesis or quadriparesis or cerebellar syndrome and/or cataracts is crucial to start early treatment and to avoid irreversible neurologic sequelae. Thus, its diagnosis requires a high

level of suspicion. Once diagnosed and treatment started, the patient can lead an almost normal life.

CASE PRESENTATION

A 32-year-old male patient was admitted with a history of recurrent generalised tonic clonic convulsions since 1 month. He had a history of convulsions since childhood which were controlled by tablet phenytoin 100 mg three times a day. There was no history of headaches or vomiting. He gave a history of proximal muscular weakness in his lower limbs. There was no sensory disturbance, ataxia or any cranial nerve involvement. He also had swellings over

Figure 1 Arrows showing large tendon xanthomas over the Achilles tendon, elbow and triceps tendon. Black arrow indicates the patient is wearing thick glasses due to aphakia.

Figure 2 Healed ulcer over the dorsum of left foot.

the back of his ankle and lateral aspect of the knee since the age of 15 years, which were progressively increasing in size. He also had an ulcer over the dorsum of his right foot 3 months back which took a long time to heal. He had a history of being operated for cataract in both the eyes 15 years back. He was a school dropout after IV standard due to poor scholastic performance. He was born of non-consanguineous marriage and the delivery was full-term and vaginal at home by a midwife. Apparently, there were no neonatal problems like hypoxia or jaundice. There was no family history of a similar disorder.

On examination, he was thin built and hypertensive. He had arcus senilis, aphakia in both the eyes due to cataract surgery with refractory correction. There was bilateral pes cavus and bilateral xanthomas affecting the Achilles tendons, the quadriceps tendon over the patella, the semitendinosus over the fibular head and the triceps tendon over the elbows (figure 1). He also had a healed ulcer over the dorsum of right foot (figure 2). He had marfanoid habitus but no other manifestations of Marfan's syndrome. He had a low IQ of 70. His speech was dysarthric. He had generalised wasting, spasticity with slight reduction of power in all the muscles. Deep tendon reflexes were brisk, and plantars were extensors. There were no cerebellar signs. There was no sensory involvement and peripheral nerves were normal.

INVESTIGATIONS

The biochemical and haematological investigations, including the lipid profile were normal. His nerve conduction studies and electromyogram were normal. He was also investigated for vasculitis but the reports were normal. CT of the brain revealed mild cerebral atrophy (figure 3). An electroencephalogram showed intermittent

sharp spiked waves. Biopsy of the soft tissue mass affecting Achilles tendon showed proliferation of xanthomatous cells without atypia or mitoses. Abundant multinucleated Touton-like giant cells were observed with a mild interstitial inflammatory component (figure 4).

DIFFERENTIAL DIAGNOSIS

In this patient of epilepsy, the most notable feature was the presence of multiple xanthomatous swellings. Multiple xanthomatosis: Tendinous, tuberous or subcutaneous is seen in familial hypercholesterolemia type II, acquired hyperlipidemias, type II diabetes mellitus, sitosterolemia, Smith Lemli Opitz syndrome (SLOS) and cerebrotendinous xanthomatosis. However classical tendon xanthomas are seen in cerebrotendinous xanthomatosis, familial hypercholesterolemia type II A and sitosterolemia; the commonest site being the Achilles tendon. Hypercholesterolemias, both congenital and acquired were ruled out as the patient's lipid profile was normal viz. serum cholesterol-4.52 mmol/l (normal upto 5.17 mmol/l), serum triglyceride-1.49 mmol/l (normal upto 1.69 mmol/l), serum high density lipoprotein-1.19 mmol/l (normal 1.03–1.55 mmol/l) and serum low density lipoprotein-2.79 mmol/l (optimal<2.59 mmol/l). His blood glucose levels, both fasting and postprandial were normal. Considering his history, he was thought to have a familial disorder. Sitosterolemia² may share several clinical characteristics with cerebrotendinous xanthomatosis, such as the development of tendon xanthomas in the first 10 years of life and the development of premature atherosclerosis. In addition, patient may have arthritis, splenomegaly and haemolytic episodes. Also, the patient may develop premature coronary artery disease which is the major cause of mortality and morbidity. Diagnosis is usually made by demonstration of very high levels of plant

Figure 3 CT of head showing mild cerebral atrophy with white matter changes and dilated ventricles.

sterols. Except for xanthomas, our patient did not have any other clinical feature of sitosterolemia.

Smith Lemli Opitz syndrome (SLOS, or 7-dehydrocholesterol reductase deficiency)³ is an autosomal recessive metabolic and developmental congenital disorder that causes the inability to correctly produce or synthesise cholesterol due to a low occurrence of the 7-dehydrocholesterol reductase enzyme. The signs and symptoms of SLOS syndrome vary widely. Mildly affected individuals may have only minor physical abnormalities with learning and behavioural problems. But these patients usually have microcephaly, hypotonia, hearing and speech difficulties. Syndactyly or polydactyly with congenital heart disease may occur. Premature cataracts are also common. The differentiating feature from cerebrotendinous xanthomatosis is that these patients have hypocholesterolemia.

Out of the four clinical criteria of cerebrotendinous xanthomatosis viz. chronic intractable diarrhoea, bilateral cataracts, multiple xanthomas and neurological symptoms, the patient had all except intractable diarrhoea. The commonest neurological abnormality seen in cerebrotendinous xanthomatosis is intractable cerebellar ataxia, which was not seen in our patient. But he had spasticity, dysarthria and mental retardation. Hence with a high suspicion of cerebrotendinous xanthomatosis, biopsy from the xanthomas was performed and the diagnosis was confirmed histopathologically.

TREATMENT

Patient could not be treated with chenodeoxycholic acid as it was not available in India and he could not afford imported tablets. He was given 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors viz. atorvastatin and ursodeoxycholic acid tablets but there was no response. Subsequently, he was treated symptomatically by phenytoin and phenobarbitone for his seizures, and by enalapril for his hypertension.

OUTCOME AND FOLLOW-UP

Patient continues to have slow deterioration of neurological status and is still under follow-up.

DISCUSSION

We made the diagnosis of cerebrotendinous xanthomatosis based on clinical, radiological and histological features. Cerebrotendinous xanthomatosis is a rare genetic metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurological abnormalities.

More than 300 patients have been diagnosed worldwide, with an estimated prevalence of 1 case per 50 000 individuals in white populations.⁴ Cases have been reported in China, Canada, Belgium, Brazil, Saudi Arabia, India, Germany, Taiwan, France, Switzerland, South Africa, Australia, Israel and Argentina; a large representation has been reported among Scandinavian populations, as well as

Figure 4 Histological features of tendinous xanthomatosis: showed proliferation of xanthomatous cells without atypia or mitoses. Abundant multinucleated Touton-like giant cells were observed with a mild interstitial inflammatory component. Arrows show foamy cells.

in Italy and Japan. A founder effect and high rate of consanguinity appear to be responsible for a high prevalence among the Druze.⁵ The disease was first described in 1937 by Van Bogaert and colleagues and has since been characterised clinically, biochemically and genetically.⁶ In 1968, Menkes *et al* described the accumulation of cholestanol, the primary metabolite found in elevated concentrations in cerebrotendinous xanthomatosis, in tissues of the central nervous system.⁷ In 1971, Salen found that chenodeoxycholic acid (CDCA), an important bile acid, was virtually absent in patients with clinical symptoms of the disease.⁸ This led to successful trials of therapy with CDCA replacement by Salen and colleagues in 1975.⁹ In 1980, defects in mitochondrial 27-hydroxylase were implicated in the biochemical pathophysiology of the disease by Oftebro *et al*.¹⁰ In 1991, mutations in the gene CYP27A1 were discovered as causative.^{4 11 12} Since then, more than 50 mutations have been implicated.¹³

Typically, the disease begins in infancy with chronic diarrhoea. Intractable diarrhoea can be a major manifestation during childhood, which was absent in our case. Cataracts become evident in childhood or adolescence, and xanthomata develop in the second and third decades of life. Significant neurological impairment also occurs; this often includes seizures, dementia and extra pyramidal dysfunction and typically begins in the third decade of life and progresses until death, often in the sixth decade of life if the condition goes untreated. Bilateral cataracts associated with chronic diarrhoea may be the earliest clinical manifestations.¹ Clinical presentations may vary considerably in cerebrotendinous xanthomatosis, but no genotype-phenotype relationship has been documented. Patients usually present in childhood or early adult life. The triad of progressive spinocerebellar ataxia, pyramidal signs and mental retardation is seen, in the large majority of patients with cerebrotendinous xanthomatosis, and mental retardation is seen in over 90%. Cataracts are present in 76% and are generally seen as early as 5–6 years.¹⁴ Seizures

are encountered in 40%–50%, and can be the presenting symptom.¹⁵ A sensori-motor neuropathy has also been documented.¹⁶

Xanthomas usually develop in adult life on the Achilles or other tendons. The cholesterol and triglycerides concentration in serum are normal, but cholestanol levels in serum and erythrocytes are elevated. Bile acid production is reduced, although the activity of the rate-limiting enzyme of bile production is elevated.⁸ CT reveals the presence of hypodense nodules in the cerebellum, and diffuse white matter hypodensity. MRI demonstrates demyelination in cerebral and cerebellar white matter. Gross examination of the brain usually reveals mild cortical atrophy,¹ especially of the frontal lobes. Gross examination of the cerebellum reveals granulomatous lesions in the white matter and atrophy of adjacent cerebellar folia. Microscopic examination of the cerebellum reveals profound demyelination; in some areas, cystic spaces of varying size may contain mononucleated cells with vacuolated eosinophilic, foamy cytoplasm. Needle like clefts are present in some of the cystic spaces, suggesting the presence of cholesterol. Other studies of the cerebellum have revealed marked loss of Purkinje cells.¹⁴ The presentation and course widely varies,¹³ and treatment can dramatically alter the natural history, especially with early initiation. Thus, a great degree of suspicion is essential to clinch the diagnosis. Tendon xanthomas, especially over the Achilles tendon are characteristic of the disorder and clinically resemble those seen in familial hypercholesterolemia but biochemical analysis reveals that they contain high amounts of cholestanol and little cholesterol. Mental retardation and progressive spasticity may develop. Some patients may develop psychiatric manifestations like dementia, depression and dysthymia.¹⁷ In the absence of typical clinical features like tendon xanthomas, Marinesco–Sjogren syndrome which is characterised by triad of cerebellar ataxia, congenital cataract and mental retardation should be considered.¹⁸ Several patients with cerebrotendinous xanthomatosis

develop premature atherosclerosis and consequent cardiac events including myocardial infarction. Several modes of treatment have been forwarded for cerebrotendinous xanthomatosis. Since 1975, chenodeoxy cholic acid (750 mg daily) has been commonly used as the standard therapy, which influences the negative feedback of cholesterol and bile acid synthesis. There is a considerable decrease in the serum cholestanol and a sharp decline in the excretion of urine bile alcohols which is associated with improvement in the clinical symptoms.¹⁹ Removal of the Achilles tendon xanthomas may be considered for cosmetic reasons, but it may worsen the gait. Long-term treatment may arrest or even reverse the progression of the disease, which may coincide with the normalisation of plasma and cerebrospinal fluid cholestanol levels. The need for early diagnosis is well-documented in the literature, as it prevents significant morbidity and mortality associated with this disease. Unfortunately, as in our case, the disease is not usually diagnosed before the second or third decade of life, and at this stage cholestanol has already been extensively deposited in many tissues. Therefore, early diagnosis of this rare metabolic disease is mandatory and cerebrotendinous xanthomatosis should be considered in every patient with intellectual impairment, spastic ataxic signs, juvenile cataract and tendon xanthomas and MRI should be done as soon as possible.

Learning points

- ▶ Cerebrotendinous xanthomatosis is a rare disease with diverse manifestations.
- ▶ Presence of any two of the following viz. chronic diarrhoea, ocular manifestations, tendinous xanthomas, neurological deficit with a normal lipid profile should make you think of the disease.
- ▶ Early treatment with chenodeoxycholic acid can immensely improve the patient's quality of life.

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Patient consent Obtained.

REFERENCES

1. **Federico A**, Dotti MT. Cerebrotendinous xanthomatosis. In: Vinken PJ, Bruyn GW, Moser HW, eds. *Handbook of Clinical Neurology*. Amsterdam: Elsevier Science 1996;**66**:599–613.
2. **Steiner RD**. Sitosterolemia. [online] Available from: <http://www.emedicine.com/ped/topic2110.htm> (accessed on 31 May 2011).
3. **Kelly RI**. Smith Opitz Lemli Syndrome. http://www.hopkinsmedicine.org/cms/SLOS_Web_Text.html#SLOS%20Summary (accessed 31 May 2011).
4. **Gallus GN**, Dotti MT, Federico A. Clinical and molecular diagnosis of cerebrotendinous xanthomatosis with a review of the mutations in the CYP27A1 gene. *Neural Sci* 2006;**27**:143–9.
5. **Leitersdorf E**, Safadi R, Meiner V, et al. Cerebrotendinous xanthomatosis in the Israeli Druze: molecular genetics and phenotypic characteristics. *Am J Hum Genet* 1994;**55**:907–15.
6. **Van Bogaert L**, Scherer HJ, Epstein E. *Une Forme Cerebrale De La Cholesterinose Generalisee* [dissertation/master's thesis]. Paris: Masson et Cie 1937.
7. **Menkes JH**, Schimschock JR, Swanson PD. Cerebrotendinous xanthomatosis. The storage of cholestanol within the nervous system. *Arch Neurol* 1968;**19**:47–53.
8. **Salen G**. Cholestanol deposition in cerebrotendinous xanthomatosis. A possible mechanism. *Ann Intern Med* 1971;**75**:843–51.
9. **Salen G**, Meriwether TW, Nicolau G. Chenodeoxycholic acid inhibits increased cholesterol and cholestanol synthesis in patients with cerebrotendinous xanthomatosis. *Biochem Med* 1975;**14**:57–74.
10. **Oftbro H**, Björkhem I, Skrede S, et al. Cerebrotendinous xanthomatosis: a defect in mitochondrial 26-hydroxylation required for normal biosynthesis of cholic acid. *J Clin Invest* 1980;**65**:1418–30.
11. **Clayton PT**, Verrips A, Sistermans E, et al. Mutations in the sterol 27-hydroxylase gene (CYP27A) cause hepatitis of infancy as well as cerebrotendinous xanthomatosis. *J Inher Metab Dis* 2002;**25**:501–13.
12. **Sugama S**, Kimura A, Chen W, et al. Frontal lobe dementia with abnormal cholesterol metabolism and heterozygous mutation in sterol 27-hydroxylase gene (CYP27). *J Inher Metab Dis* 2001;**24**:379–92.
13. **Gonzalez-Cuyar LF**, Morrison AL, Perry G, et al. Cerebrotendinous xanthomatosis: a critical update. *Future Neurology* 2008;**3**:491–501.
14. **Ko KF**, Lee KW. Cerebrotendinous xanthomatosis in three siblings from a Chinese family. *Singapore Med J* 2001;**42**:30–2.
15. **Arlazaroff A**, Roitberg B, Werber E, et al. Epileptic seizures as a presenting symptom of cerebrotendinous xanthomatosis. *Epilepsia* 1991;**32**:657–61.
16. **Kuritzky A**, Berginer VM, Korczyn AD. Peripheral neuropathy in cerebrotendinous xanthomatosis. *Neurology* 1979;**29**:880–1.
17. **Lee Y**, Lin PY, Chiu NM, et al. Cerebrotendinous xanthomatosis with psychiatric disorders: report of three siblings and literature review. *Chang Gung Med J* 2002;**25**:334–40.
18. **Sieber HR**, Berndt S, Conrad B. Cerebrotendinous xanthomatosis with out tendon xanthoma mimicking Marinesco Sjogren syndrome: a case report. *J Neurol Neurosurg Psychiatry* 1996;**60**:582–5.
19. **Berginer VM**, Salen G, Shefer S. Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. *N Engl J Med* 1984;**311**:1649–52.

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