

Cerebrotendinous xanthomatosis with cholestanolaemia — involvement of five individuals in a Malay family

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Summary

Cerebrotendinous xanthomatosis (CTX), a rare inherited lipid storage disease is due to a defect in bile acid metabolism. Involvement of five members of a family is presented. The clinical features, laboratory and pathologic findings are discussed. Tendinous and tuberous xanthomatosis, bilateral cataracts, cerebral impairment and raised serum cholestanol are the salient features. We believe this is the first report of CTX in Malaysia.

Key words: Cerebrotendinous xanthomatosis, cholestanolaemia, involvement of five individuals in a Malay family.

Introduction

In 1937 Van Bogaert, Scheren and Epstein described a disease characterised by distinct symptoms such as dementia, ataxia, cataracts and xanthomas.^{1,2,3} The clinical features of CTX are insidious and unpredictable. The initial stage usually begins in childhood and is characterised by mental retardation or a decrease in intellectual functions. Juvenile cataracts are seen during adolescence or early adulthood. Tendon xanthomas have been observed in the second decade but usually are not noticed until the third or fourth decades, the Achilles tendon being the most common site. Death usually results from progressive neurologic deterioration.

CTX is an autosomal recessive disorder. The underlying biochemical defect is a deficiency of C27 steroid 26 – hydroxylase,⁴ an important enzyme in the synthesis of bile acids.⁵ The serum, bile, urine, xanthomatous tissue and cerebrospinal fluid (CSF) of these patients show raised cholestanol levels, with either low or normal serum cholesterol levels.^{1,3,6}

To the best of our knowledge CTX has not been reported in Malaysia. Compared to other cases of CTX reported in the literature world-wide to date, this report records what is possibly the largest number of individuals with CTX in a single family.^{1,2}

Case Report

M.A.O, a 36 year old Malay male presented to the Orthopaedic Unit with a complaint of progressive swelling of the right Achilles tendon. The swelling became ulcerated and infected for

the last week prior to admission. Clinical suspicion of a malignant neoplasm led to the excision of the swelling. The excised lesion was subjected to histopathological examination.

Discrepancies between the histological findings and the clinical diagnosis led to a more thorough study of the case with regard to history, clinical examinations and laboratory investigations.

The patient had been complaining of the progressive tendoachilles swelling for the past 30 years. A similar swelling of the left Achilles tendon had been excised the year before the current admission. Family history obtained from M.A.O's mother showed that a brother, a sister and an uncle were also afflicted with progressive bilateral swelling of the Achilles tendon since they were seven to 10 years old. Another sister had similar lesions but had died a few years previously due to upper abdominal pain and fever of one week duration. These family members had poor vision since young and were mentally retarded. M.A.O's father (deceased) and mother were first cousins. Neither parent had the symptoms mentioned.

Clinical examination of M.A.O showed short stature, mild pallor and bilateral cataracts. He had subnormal intelligence. There was a fresh scar on the right ankle resulting from the recent surgical excision of the suspected neoplasm mentioned earlier. The left leg also showed a longitudinal scar and a palpable swelling 4 x 5 cm in the region of the Achilles tendon. Bilateral, symmetrical single subcutaneous nodules, 1cm in diameter were also seen on the extensors of his elbows.

Histological examination of the recently excised ankle swelling measuring 18 x 9cm and the elbow nodules revealed xanthomas (Fig. 1). These were composed of numerous sterol clefts, foamy histiocytes, multinucleated giant cells of foreign body and touton types and were associated with extensive fibrosis and hyalinisation of collagen. The vessels showed no atherosclerotic changes. Immunoperoxidase staining for a variety of histiocytic markers were negative.

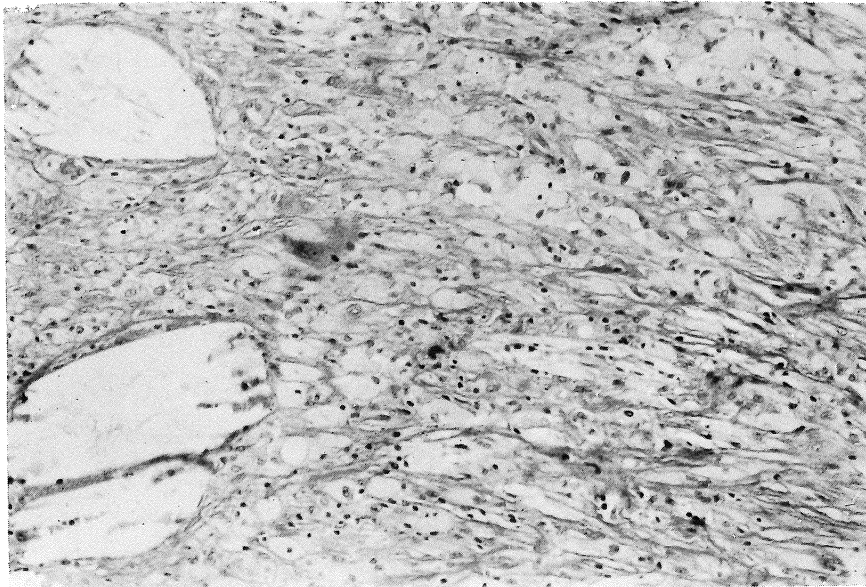


Fig. 1 Histopathology of CTX: areas of xanthomatisation, adjacent to sterol clefts.

Laboratory study of M.A.O showed mild anaemia and increased erythrocyte sedimentation rate (ESR). Serum levels for glucose, cholesterol, lipoproteins, uric acid and calcium were within normal limits as was the serum protein electrophoresis profile. The puzzling data gathered thus far was transmitted to a colleague abroad. This led to the suggestion of a disease resulting from storage of unusual sterol(s). Serum and urine of M.A.O were lyophilised and sent abroad for sterol analysis by gas – liquid chromatography (GLC). This showed a markedly elevated serum concentration of an unusual sterol, cholestanol, of 0.1 mmol/L (Normal (0.003–0.015 mmol/L)). The test also confirmed a normal serum cholesterol concentration of 4.40 mmol/L (normal range 3.63–8.03 mmol/L). The findings of raised serum cholestanol coupled with normal serum cholesterol were consistent with a diagnosis of cerebrotendinous xanthomatosis (CTX).

Other members of M.A.O's family complaining of swelling in the tendoachilles were also subjected to further scrutiny (Fig. 2). Physical examination showed that a 30 year-old brother (S5), a 27 year-old sister (S7) and a 54 year-old uncle (I.A) also had bilateral tendoachilles swellings ranging from eight to 20 cm in longitudinal diameter (Figs. 3, 4). Subcutaneous nodules 1 cm in diameter were seen on the extensors of both elbows in S7 (Fig. 5) and on the back plus the inner right thigh of I.A. Surgical scars resulting from excision of elbow nodules were seen in S5. The left big toe of I.A had been amputated due to a toe swelling 20 years previously. S5, S7 and I.A had bilateral cataracts and were mentally subnormal. I.A was found to have dementia. Of the remaining family members, a 28 year-old brother (S6) had bilateral cataracts and mental retardation but not leg swelling or subcutaneous nodules. M.A.O's mother and other living siblings were normal. The family pedigree (Fig. 2) suggested the occurrence in this family of an autosomal recessive disorder inherited in Mendelian fashion.

The histopathology of elbow nodules removed from S5 was reviewed. They showed similar findings to those obtained for M.A.O's lesions. The previous toe biopsy from I.A reported then as a 'neurofibroma' was however not available for review.

Biochemical investigations carried out on S5, S6, S7 and I.A gave findings similar to those for M.A.O. Sterol analysis by GLC showed markedly raised serum cholestanol concentrations of 0.06–0.09 mmol/L coupled with normal or low-normal serum cholesterol concentrations of 3.44 to 5.73 mmol/L. CTX was subsequently diagnosed in S5, S6, S7 and I.A. This family therefore had a total of five members proven to be afflicted with CTX.

Fig. 2. Pedigree of Cerebrotendinous xanthomatosis in one Malay family in Penang

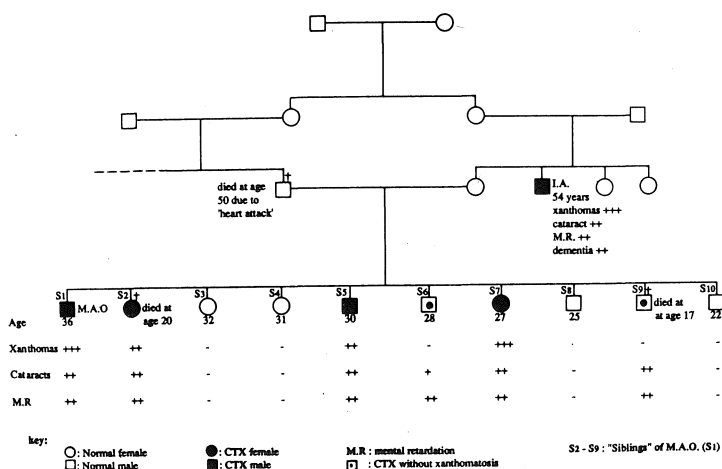


Fig. 2. Pedigree of cerebrotendinous xanthomatosis in one Malay family in Penang



Fig. 3. Bilateral, symmetrical xanthomatosis of the Achilled tendon in S7.



Fig. 4. Massive tendoachilles xanthomatosis, facies showing mental retardation and bilateral cataracts in the uncle.



Fig. 5. Tuberous xanthoma of the elbow in S7.

Discussion

CTX is a rare disease. From its initial discovery in 1937 to 1983 only 53 cases were reported world wide.⁷ By 1989, the number had risen to at least 144.⁸ The rapid increase in diagnoses of CTX reflects an increasing awareness on the part of clinicians and an improvement in laboratory diagnostic capability. To the best of our knowledge, our five cases represent the first report of CTX in Malaysia. It is possible that CTX, although rare, has been underdiagnosed in this country. With this in mind, we would like to highlight several aspects of our cases reported.

The primary patient M.A.O had a long history of the complaint and a family history suggestive of an autosomal recessive Mendelian disorder. There were striking clinical features such as mental retardation as well as surprisingly normal results for several biochemical tests including serum cholesterol. In spite of the presence of these classical features of CTX, the study of our patient proved difficult and lengthy. This illustrates the usefulness of a thorough patient and family history. The suspicion of a neoplasm in M.A.O could have been excluded at the outset by knowledge of the long duration and bilateral nature of his ankle swelling. Difficulty in obtaining a thorough patient and family history from M.A.O was due to the mental retardation usually seen in CTX. Much progress was made during our study by interviewing the mother thus overcoming this basic difficulty.

The xanthomatous nature of M.A.O's tendinous lesion as shown by histological examination indicated the occurrence of a lipid storage disorder. The discovery of tendon xanthomas alone cannot be used to infer a high probability for the occurrence of CTX as these lesions are common to many hyperlipoproteinaemic disorders, the most common cause being familial hypercholesterolaemia.⁹ However, associated with the tendoachilles xanthoma of M.A.O were juvenile cataracts, mental retardation, an autosomal recessive pattern of inheritance and perhaps even more relevant, a normal value for serum cholesterol. These findings were sufficient to exclude familial hypercholesterolaemia. It has been suggested that low or normal serum cholesterol levels in combination with the above symptoms mandates that cholestanol also be measured to confirm CTX,⁷ raised serum cholestanol being the most important diagnostic feature. This finding in all our five patients confirms the diagnosis of CTX. However, if familial hypercholesterolaemia and CTX had been excluded in a patient presenting with tendon xanthomas since young, then sitosterolaemia with xanthomatosis should be considered.⁷

This is a rare disorder characterised by storage of plant sterols. With regard to clinical manifestations of CTX, the affected family members showed minor variations. S6 appeared not to have had any tendon xanthomas which usually is an almost essential feature of CTX. The history and circumstances surrounding the deaths of two siblings and the father in this family raises interesting speculations. The upper abdominal pain in S2 could have been due to gall stones, while the history of poor vision in S9 could have been due to juvenile cataracts. Juvenile cataracts and gall stones are clinical features of CTX.³ Therefore these two deceased siblings could also have suffered from CTX, although this was not proven.

This study has already proven that four out of the total ten siblings were afflicted with CTX. Assuming both parents to be heterozygous for CTX, the usual pattern of autosomal recessive inheritance seemed to have resulted in an unfortunately high proportion of affected siblings. If S2 and S9 were in fact affected by CTX, the proportion of affected siblings would be even higher. This high proportion would be more easily understood if one of the patients was homozygous for CTX. It is interesting to note that the father died at the age of 50 of 'heart attack'. Myocardial infarction is a feature of CTX.⁷ If the father was homozygous for CTX, all siblings unaffected by CTX would have to be heterozygous carriers.

With regard to treatment, we plan to have our patients treated with chenodeoxycholic acid or cholic acid (750 mg to 1000 mg daily). Both have shown some degree of effectiveness by way of reducing serum cholestanol levels.¹⁰ However, because many CTX patients including those in our study present themselves late when the sterol storage problem has done some irreversible damage, this mode of treatment can at best only be expected to prevent further deposition of sterols in the tissues. Excision of the right ankle swelling with the attached Achilles tendon in our patient M.A.O seemed advantageous for cosmetic reasons but it worsened his gait as a result of loss or damage to the tendon. Furthermore, the effectiveness of excising the swelling is questionable as shown by the recurrence of swelling in M.A.O's left ankle. It is our hope that, through this report, clinicians will be more aware of this crippling disease and will bear CTX in mind when investigating and treating cases of juvenile cataracts, tendinous xanthomatosis, atypical psychosis¹¹ or other associated symptoms described in this report.

Acknowledgement

We thank Dr. Steven Kossard of the Skin and Cancer Foundation, New South Wales, Australia for his opinions on the histopathology; Professor Gerald Salen, of the University of Medicine and Dentistry of New Jersey, USA for doing the serum cholestanol analysis; doctors of the Orthopaedic Unit, General Hospital, Penang for giving us the gross specimen and Dr. Jamal Ibrahim for assistance in preparing this manuscript. We express our deepest appreciation to the patients family for allowing us to study and report this case.

References

1. Salen G. Cholestanol deposition in Cerebrotendinous Xanthomatosis: A Possible Mechanism. *Ann Intern Med* 1971; 75: 843-851
2. Koopman BJ, Wolthers BG, Molen JC Van der, Slik W Van der, Wattereus RJ, Spreken A Van. Cerebrotendinous xanthomatosis: A Review of Biochemical Findings of the Patient Population in the Netherlands. *J Inher Metab Dis* 1988; 11: 56-74.
3. Canelas HM, Quintao ECR, Scaff M, Vanconcelos KS, Brotto MWI. Cerebrotendinous Xanthomatosis: Clinical and Laboratory Study of two cases. *Acta Neurol Scand* 1983; 67: 305-311.
4. Skrede S, Bjorkhem I, Kvittingen EA, East C, Grundy SM, Skrede S. Reduced C27 - Steroid 26 - hydroxylase Activity in Heterozygotes For Cerebrotendinous Xanthomatosis. *Scand J Clin Invest* 1988; 48: 425-429.
5. Bavinck JNB, Vermeer BJ, Leuven JAG, Koopman BJ, Wolthers BG. Capillary Gas Chromatography of Urine Samples in Diagnosing Cerebrotendinous xanthomatosis. *Arch Dermatol* 1986; 122: 1269-1272.
6. Salen G, Grundy SM. The Metabolism of Cholestanol, Cholesterol and Bile Acids in Cerebrotendinous Xanthomatosis. *J Clin Invest* 1973; 52: 2822-2835.
7. Salen G, Shefer S, Berginer VM. Familial diseases with storage of sterols other than cholesterol: cerebrotendinous xanthomatosis and sitosterolemia with xanthomatosis. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS eds. *The metabolic basis of inherited disease*, 5th ed. New York: McGraw-Hill, 1983: 713-730.
8. Matsumuro K, Takahashi K, Matsumoto H, Okatsu Y, Kuryama M. A case of cerebrotendinous xanthomatosis with convulsive seizures. *Rinsho Shinkeigaku* 1990; 30(2): 207-209.
9. Cruz PD, Jr, East C, Bergstresser PR. Dermal, subcutaneous, and tendon xanthomas: Diagnostic markers for specific lipoprotein disorders. *J Am Acad Dermatol* 1988; 19: 95-111.
10. Koopman BJ, Wolthers BG, Van Der Molen JC, Waterreus RJ. Bile acid therapies applied to patients suffering from cerebrotendinous xanthomatosis. *Clin Chim Acta* 1985; 152: 115-122.
11. Berginer VM, Foster NL, Sadowsky M, Townsend III JA, Siegel GJ, Salen G. Psychiatric Disorders in Patients With Cerebrotendinous Xanthomatosis. *Am J Psych* 1988; 145: 354-357.