Case Report

A Case of Cerebrotendinous Xanthomatosis: Effects of Ursodeoxycholic Acid Administration on Serum Bile Acids and Cholestanol

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Cerebrotendinous xanthomatosis (CTX) is a rare familiar disease characterized by tendon xanthomas, cataracts, cerebellar ataxia, dementia and an elevated serum cholestanol level. In this paper, a 50-year-old man with typical signs and symptoms of CTX is described. Serum cholestanol and chelesterol concentrations were 17.9-28.6 μg/ml and 109-153 mg/dl, respectively. The determination of non-sulfated bile acid concentration in the serum assayed by mass fragmentography disclosed an abnormal profile. The concentration of cholic acid (0.30-0.52 μg/ml) was higher than normal, while those of chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid and lithocholic acid were extremely low or undetectable. Administration of ursodeoxycholic acid (300 mg per day, orally) for 2 weeks resulted in a marked reduction of serum cholic acid concentration. However, serum cholestanol levels remained unchanged.

Key words; Tendon xanthoma, Cholesterol, Cholic acid.

Cerebrotendinous xanthomatosis (CTX) is a rare but well-defined familiar disease characterized by tendon xanthomas, cataracts, progressive cerebellar ataxia, dementia and an elevation of serum cholestanol with normal level of cholesterol[1].

Although the pathogenesis of CTX is not fully understood, deposition of cholestanol and cholesterol in various tissues is one of the major metabolic derangements of the disease[1)-3)]. Salen and his coworkers have disclosed several biochemical abnormalities in CTX; accelerated synthesis of cholesterol and cholestanol[3)-4)], and defective synthesis of cholic acid and chenodeoxycholic acid[5].

Increased levels of 25 hydroxylated bile alcohols in bile and feces have indicated that the block in bile alcohol metabolism may be causally related to the pathogenesis of CTX[6], while the site of the primary metabolic defect is still controversial[6)-8)]. The profile of biliary bile acids is well documented[8], however, that of bile acids in serum has not been established as yet. Beppu et al. observed for the first time that in CTX sera, the concentration of cholic acid was high and those of chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid and lithocholic acid were very low[9]. In the present communication, the profile of serum bile acids in a CTX patient was compared to that of biliary bile acids. In addition, the effects of an administration of ursodeoxycholic acid on the profile of bile acids and cholestanol in patient's

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sera were also reported.

CASE REPORT

A 50-year-old man (II-3 in Fig. 2) was admitted to Tsukuba University Hospital in December 1979 for evaluation of the tumors on both Achilles tendons and elbows. The tumors were first noted on the posterior aspect of both ankles and then on the elbows before six years of age. These tumors grew gradually and the ones on the Achilles tendons extended up to the lower parts of calves, covering the entire length of the Achilles tendons by the age of twenty. They restricted the range of movement of both feet and caused difficulties in wearing shoes. His performance at school was poor. His vision has progressively deteriorated over the past 5 years.

On admission, he was healthy except for the large, hard tumors which covered both Achilles tendons and the lower parts of both calves (Fig. 1). Oval tumors 2×4 ×3 cm in size were noted on the elbows. Neurological examinations revealed slight cerebellar ataxia and moderate dementia. He had difficulty even with simple calculations. His recent memory was also poor. Electroencephalography showed continuous diffuse abnormality. Computed tomography of the brain revealed minimal atrophy of the brain, with no tumorous lesions. Serum levels of triglyceride and total cholesterol were 85 mg/dl and 153 mg/dl, respectively,

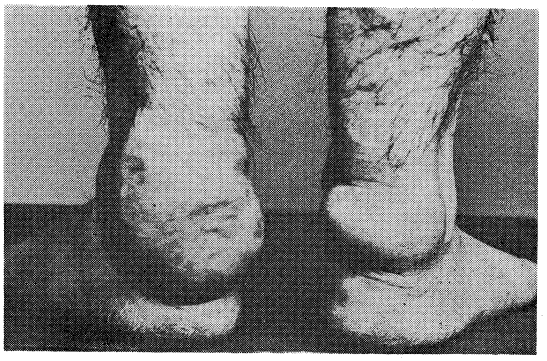

Fig. 1. A back view of Achilles tendon xanthomas seen in the present case.

whilst α-, pre β- and β-lipoproteins were 34.1%, 16.4% and 49.4%. Other routine laboratory data including complete blood count, hemogram, blood chemistry, and urinalysis were normal. Chest X-ray revealed a small peripheral lesion convex towards the lung with a sharp contours in the right upper lung field. Tomograms suggested a continuity of the tumor with the pleura. ECG findings were within normal limits. Ophthalmological examinations disclosed bilateral cataracts. After examinations and palliative surgery to the Achilles tendon xanthomas, the patient was discharged. However, he died unfortunately of a traffic accident, and the study was discontinued. An autopsy was not obtained on this patient.

Family History: There was no consanguinity. Parents were both healthy and

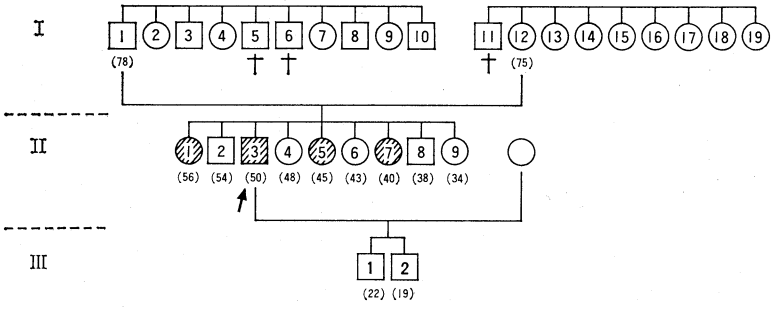

Fig. 2. Pedigree of the family. Four members had typical manifestations of cerebrotendinous xanthomatosis (shaded). The patient is indicated by an arrow. I, II and III represent the generation. Figures in parentheses indicate ages. □, male; ○, female; †, died.

Table 1. Serum Cholestanol and Cholesterol in CTX and Non-CTX Subjects

subject	cholestanol (μg/ml)	cholesterol (mg/dl)
CTX cases		
II-1 (H.I.)	10.3	181
II-3 (S.I.)	17.9	109
II-5 (M.K.)	13.0	158
II-7 (F.S.)	14.8	147
asymptomatic relatives		
I-1	2.3	189
I-3	2.8	161
I-4	3.5	220
I-12	2.0	154
II-4	trace	153
II-8	trace	153
III-1	2.5	183

Blood samples were withdrawn in the morning after an overnight fast. Numerical symbols for CTX cases and relatives correspond to those in Fig. 2.

had no xanthoma of any type. They had 9 children, 3 males and 6 females, of whom the first (H. I.), third (patient, S. I.), fifth (M. K.) and seventh (F. S.) were affected (Fig. 2). All these affected siblings had tendon xanthomas similar to those observed in the present case. Neurological signs and symptoms in these siblings were obscure except for mental retardation which was observed in all of them. The patient had 2 children, neither of whom were affected. Serum cholestanol and cholesterol levels of his relatives are summarized in Table 1.

ASSAY METHODS

Cholestanol was determined quantitatively by gas-liquid chromatography-mass fragmentography (GLC-MS) as described by Seyama et al.[10] Non-sulfated bile acids were determined by GLC-MS as described elsewhere[11].

RESULTS

The diagnosis of CTX was confirmed by a high level of serum cholestanol, 17.9 μg/ml, the mean normal control being 3.36±0.54 μg/ml[10]. The cholesterol level in the same sample was 109 mg/dl. On the 3rd hospital day, biopsy specimens were obtained from the left Achilles tendon. Macroscopically, the tumor was yellow and fused with the tendon. Microscopically, it was a xanthogranuloma with scattered giant cells surrounded by foam cells. The contents of cholesterol and cholestanol in the tumor were 100 mg/g wet weight and 3.6 mg/g wet weight, respectively.

Biliary drainage was carried out after an overnight fast. The concentrations of non-sulfated bile acids in the patient's bile (B-bile) are; cholic acid 4.26 mg/ml (91.8%), chenodeoxycholic acid 0.33 mg/ml (7.1%), ursodeoxycholic acid 0.02 mg/ml (0.4%), deoxycholic acid 0.03 mg/ml (0.6%) and lithocholic acid 0 mg/ml. In the serum obtained simultaneously with the bile, the concentrations of cholic acid and chenodeoxycholic acid were 0.52 μg/ml (86.7%) and 0.08 μg/ml (13.3%), respectively. The profiles of serum bile acids in the patient and his relatives are summarized in Table 2. Asymptomatic relatives showed essentially the same pat-

Table 2. Serum Bile Acid Composition in CTX and Non-CTX Subjects

subject	bile acid (μg/ml)					
	total	C	CDC	UDC	DC	LC
CTX cases						
II-3	0.60	0.52	0.08	0.00	0.00	0.00
II-5	0.39	0.28	0.08	0.03	0.00	0.00
II-7	0.55	0.39	0.11	0.01	0.00	0.04
mean	0.51	0.40	0.09	0.01	0.00	0.01
± SD	±0.11	±0.12	±0.02	±0.02	±0.00	±0.02
asymptomatic relatives						
I-3	1.83	0.21	0.80	0.04	0.72	0.06
I-4	1.55	0.14	0.54	0.06	0.77	0.04
I-12	1.10	0.09	0.28	0.04	0.60	0.09
mean	1.49	0.15	0.54	0.05	0.70	0.06
± SD	±0.37	±0.06	±0.26	±0.01	±0.09	±0.03

Blood samples were withdrawn in the morning after an overnight fast. C, cholic acid; CDC, chenodeoxycholic acid; UDC, ursodeoxycholic acid; DC, deoxycholic acid; LC, lithocholic acid.

Table 3. Effects of Ursodeoxycholic Acid Administration on Serum Bile Acids and Cholestanol

duration of treatment	bile acid (μg/ml)						cholestanol (μg/ml)
	total	C	CDC	UDC	DC	LC	
0	0.39	0.30	0.08	0.01	0.00	0.00	28.6
1 week	2.03	0.11	0.10	1.82	0.00	0.00	23.6
2 weeks	2.61	0.04	0.11	2.46	0.00	0.00	27.9

Ursodeoxycholic acid (300 mg/day) was administered orally in three divided doses. Blood samples were withdrawn in the morning after an overnight fast. C, cholic acid; CDC, chenodeoxycholic acid; UDC, ursodeoxycholic acid; DC, deoxycholic acid; LC, lithocholic acid.

tern as normal subjects[9,11].

Ursodexycholic acid was administered at a dose of 300 mg/day orally for 2 weeks. Serum bile acid and cholestanol concentrations before and after the administration are shown in Table 3. After ursodeoxycholic acid administration serum levels of this bile acid were markedly increased. On the other hand, the levels of cholic acid decreased markedly, whilst other bile acids did not show any appreciable change. The concentration of cholestanol remained unchanged. Diarrhea and other untoward side effects were not observed.

DISCUSSION

In the present case, the diagnosis of CTX was confirmed by the demonstration of elevated levels of cholestanol both in the serum and in the tendon xanthomas. The

serum cholestanol levels in this patient were elevated similar to levels previously reported[3]. The content of cholestanol in the tendon xanthoma of the patient was 3.6% of cholesterol, which is 10 times higher than those in xanthomas from hypercholesterolemic subjects and comparable to those in tendon xanthomas from CTX subjects[2-3]. A solid lesion disclosed in the chest X-ray film may be the sterol deposition in the pleura, though histological or biochemical exploration was not carried out. No signs of space occupying lesions were detected in computed tomography of the brain, while minimal atrophy of the brain was noted. Although the incidence of CTX among his siblings is rather high (4 out of 9), the absence of the disease in his parents and children suggests an autosomal recessive inheritance.

Consistent with a previous report[3], the relative content of bile acids in the patient's bile was abnormal and compatible with that of CTX bile; cholic acid was the major bile acid (91.8%) and chenodeoxycholic acid (7.1%) was the second one, others being insignificant. Beppu and his coworkers[9] reported that in CTX sera, chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid and lithocholic acid were low significantly, while the concentration of cholic acid was higher than that in healthy controls. The data of serum bile acids of this patient (S. I.) and his siblings (M. K., F. S.) were included in their study. The serum bile acid composition of the present case showed a characteristic pattern of CTX sera. The total bile acid level was very low. Eighty seven per cent of total bile acid was cholic acid, while chenodeoxycholic acid which is the major bile acid in normal sera was only 0.08 μg/ml or 13% of the total bile acid. Serum levels of other bile acids were negligible. This observation is applicable to the data obtained from the serum immediately before the administration of ursodeoxycholic acid. Thus, our data show that the profile of serum bile acids is similar to that of biliary bile acids, although the chenodeoxycholic acid: cholic acid ratio was higher in serum than in bile. Since the ratio in serum is still extremely low compared to that of normal sera, and as serum is more readily available than bile, the ratio and the total bile acid level in serum should be of diagnostic value as suggested elsewhere[9].

It is not known why the secondary bile acids (deoxycholic acid and lithocholic acid) are low in the bile of patients with CTX. However, as the secondary bile acids in serum are also low in our patient, it is unlikely that the excretion of secondary bile acids into bile is impaired in this disease. The disturbance of chenodeoxycholic acid production and the low concentration of chenodeoxycholic acid in serum and bile may be responsible for a decreased concentration of lithocholic acid in CTX. However, this assumption would not explain the decreased concentrations of deoxycholic acid in serum and bile because the major biliary bile acid in our patient was cholic acid which was rather higher than normal. Two possibilities could account for this finding. One that the bacterial conversion of primary bile acids into secondary bile acids is disturbed, or secondarily, that the absorption of secondary bile acids may be disturbed. The latter possibility seems less likely because ursodeoxycholic acid administered orally was absorbed in the present case and so was chenodeoxycholic acid in a previous report[12].

Oral administration of chenodeoxycholic acid is reported to reduce the cholestanol concentration in serum of CTX patient[12]. In the present study, ursodeoxycholic acid was administered to the patient because ursodeoxycholic acid but not chenodeoxycholic acid was approved for clinical use. Under the present condition, the administration of ursodeoxycholic acid failed to produce a substantial decline in serum cholestanol level. However, it caused a marked decline of cholic acid concentration in serum. The decline of cholic acid may be a result of the repression of cholesterol

synthesis and bile acid production by ursodeoxycholic acid[13], which suggests the preservation of the feed-back mechanism of bile acid production in CTX patients. If the increased synthesis of cholestanol in CTX is a result of the decreased bile acid production as suggested previously[3], the elevation of total serum bile acid concentration by ursodeoxycholic acid administration may normalize the increased production of cholestanol in CTX patients. Although this is not the case in the present study, long-term treatment is necessary for the evaluation of the therapeutic use of this bile acid.

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