

Case reports

Isolated co-lipase deficiency in two brothers

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SUMMARY Two normally developed Assyrian brothers with isolated pancreatic co-lipase deficiency are described. They presented at the age of 5-6 years with loose stools. They had steatorrhoea, and analysis of exocrine pancreatic enzymes in the small intestine showed co-lipase deficiency, while amylase, chymotrypsin, trypsin, and lipase were normal. Intraduodenal infusion of purified co-lipase improved fat digestion measured by the triolein breath test. Their steatorrhoea diminished on treatment with enteric-coated pancreatic enzymes.

The first indication for the existence of a co-factor for pancreatic lipase was reported in 1963.¹ In 1969 a heat-stable co-factor was separated from lipase by gel-filtration.² Pure pancreatic lipase is inhibited by bile salts in concentrations over their critical micellar concentrations.³ The function of the co-factor, called co-lipase, is to restore lipase activity in the presence of bile salt. In man lipase and co-lipase are present in equimolar concentrations in the duodenum.⁴ Isolated lipase deficiency was first described in four children by Sheldon in 1964.⁵ Since then another eight patients with lipase deficiency have been reported.⁶⁻¹³ This report describes the first two cases of isolated co-lipase deficiency in two Assyrian brothers.

Methods

PANCREATIC ENZYME ACTIVITIES AND BILE SALT CONCENTRATIONS

The patients were intubated with a polyethylene cannula according to standard procedures. Content was collected from the first part of the jejunum. One unit per kilogram body weight of cholecystokinin-pancreozymin (CCK-PZ) was given in a slow intravenous injection. Intestinal contents were collected by siphonage in three 10 minute and one 30 minute fractions. They were collected over ice and frozen until analysed. The test was done three times in the older brother, the time between the first and the third test being two years. In the younger brother and in both parents the test was done once.

Amylase was assayed spectrophotometrically with soluble starch as substrate.¹⁴ Trypsin and chymotrypsin

activities were assayed titrimetrically¹⁵ using p-tosyl-L-arginine methyl ester (TAME) and N-acetyl-L-tyrosine ethyl ester (ATEE), respectively, as substrates. Lipase and co-lipase were measured titrimetrically using tributyrates as substrate.⁴ Total bile salt concentrations and the ratio of glycine- to taurine-conjugated bile salts were assayed enzymatically after extraction from duodenal contents and separation by thin-layer chromatography.¹⁶

TRIOLEIN BREATH TEST

After an overnight fast 5 μ Ci ¹⁴C-labelled triolein in 100 ml 10% Intralipid flavoured with chocolate was taken as a drink. The patient stayed resting in bed for 10 hours from the start of the test. Breath CO₂ was collected at zero time and hourly for 10 hours and ¹⁴CO₂ was analysed.¹⁷ Two months later the test was repeated with the same test meal by mouth. This time 10 mg purified porcine co-lipase¹⁸ was infused intraduodenally through a polyethylene cannula during the first two hours. Output of ¹⁴CO₂ was calculated as percentage dose per hour. The breath test was done only in the older brother.

FAT BALANCE

A standardised diet was given and stools collected for four days. Faecal fat was estimated chemically.¹⁹ Fat balance was carried out twice in both brothers with no extra pancreatic enzymes and on supplementation with enteric-coated pancreatic enzymes, Pancrease^R.

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Two Assyrian brothers are described. They were born in Lebanon. Since 1976 they have lived in Sweden. Their parents are first cousins. There is no family history of loose stools.

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CASE 1

J C was born in 1971. He was breastfed for four months. His mother describes him as always tired and with a bad appetite. There was no history of loose stools or jaundice until 1977 when he was first seen by us. He had then had loose stools for some months. He was a healthy boy and showed appropriate height and weight. Apart from finger clubbing the physical examination was normal. An initial laboratory examination showed moderately increased liver transaminases but normal haemoglobin, leucocytes, and thrombocytes. His sweat-test was normal. He had a steatorrhoea. A test for pancreatic function showed an isolated co-lipase deficiency but was otherwise normal (Table).

Treatment with pancreatic enzymes and fat-soluble vitamins was started and his stools became normal. During the following three years he had periods of tiredness and bouts of jaundice. During the jaundice he had raised concentrations of bilirubin, transaminases, and polyclonal gammaglobulins in serum. He was HBsAg-negative but he had antibodies to hepatitis A and to hepatitis B, HBsAg subtype d. Ultrasonography of the abdomen revealed gall stones. A percutaneous needle biopsy showed active portal liver cirrhosis. During the third year of observation he developed anaemia, granulocytopenia, and thrombocytopenia. His bone marrow was megaloblastic. Vitamin B12 in serum was subnormal. He had no intrinsic factor deficiency. All laboratory signs of pancytopenia disappeared after start of treatment with injections of vitamin B12.

CASE 2

B C, younger brother of J C, was born in 1974. He was breastfed for four months. He was healthy until 1979 when he developed loose fatty stools. Physical examination was normal and his height and weight were appropriate. He had normal serum concentrations of haemoglobin, leucocytes, thrombocytes, vitamin B12, and liver tests. His sweat-test was normal. He had a steatorrhoea and the test for pancreatic function was

similar to his brother's (Table). Ultrasonography showed gall stones. His stools improved on pancreatic supplementation. During the last year he had unexplained episodes of fever and developed a chronic mucocutaneous candidiasis. Apart from a polyclonal hypergammaglobulinaemia his blood tests have remained normal. Tests for immunodeficiency and immune complex diseases were negative. A percutaneous needle liver biopsy was histologically normal.

Results

PANCREATIC ENZYME ACTIVITIES AND BILE SALT CONCENTRATIONS

The different pancreatic enzyme activities after CCK-PZ stimulation are shown in the Table. Both brothers had normal amylase, trypsin, chymotrypsin, and lipase activity. The activities of co-lipase were subnormal in all samples in both brothers, and about 10% of normal co-lipase activity in children of this age (Fig. 1). There were no differences in the three tests done on the older boy. Both parents had normal enzyme activities including co-lipase.

Normal amounts of total bile salt concentrations were found in both children. The increase of the total bile salt concentrations after the injection of CCK-PZ points to a normal function of the gall bladder. The ratio of glycine- to taurine-conjugated bile salts was increased. The older brother had a ratio of 9.6 and the younger brother a ratio of 4.3 (normal range 1.3–4.0).

TRIOLEIN BREATH TEST

The breath test in the older boy with and without co-lipase intraduodenally is shown in Fig. 2. With no extra enzyme supplementation the boy had a maximal peak of $^{14}\text{CO}_2$ after six hours. When purified co-lipase was given intraduodenally the maximal peak occurred earlier — that is, after three hours — and the peak value was higher.

Table Pancreatic enzyme activities, amylase, chymotrypsin, trypsin, lipase and co-lipase, and total bile salt concentrations in small intestinal content

Min	Amylase (E/ml)	Chymo- trypsin ($\mu\text{mol}/\text{min}/\text{ml}$)	Trypsin	Lipase	Co-lipase	Total bile salt (mmol/l)
JC						
10	393	60	30	1580	120	3.8
20	451	90	90	2870	324	35.2
30	378	60	54	2240	206	11.1
60	395	65	55	1900	204	11.5
BC						
10	595	195	92	2816	120	2.5
20	484	120	98	1992	343	18.4
30	486	140	113	2276	352	22.4
60	186	26	39	654	350	3.0
Normal range (age 1–22 years)	73–370	60–215	55–160	718–4320	848–3252	5.8–39.6

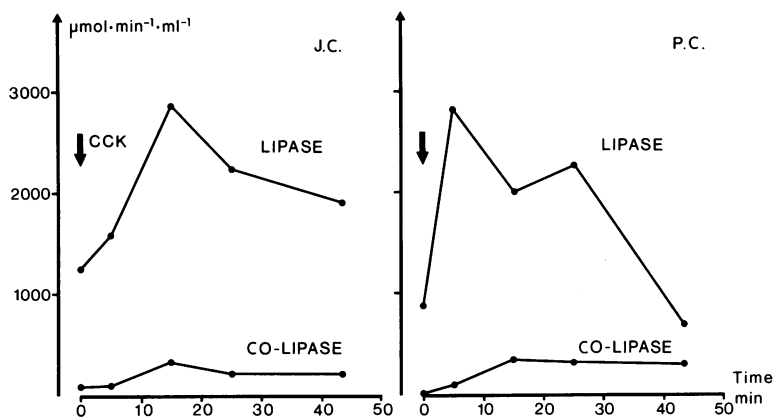


Fig 1 Cases 1 and 2. Activities of lipase and co-lipase ($\mu\text{mol/l}$) in small intestinal content after stimulation with CCK-PZ.

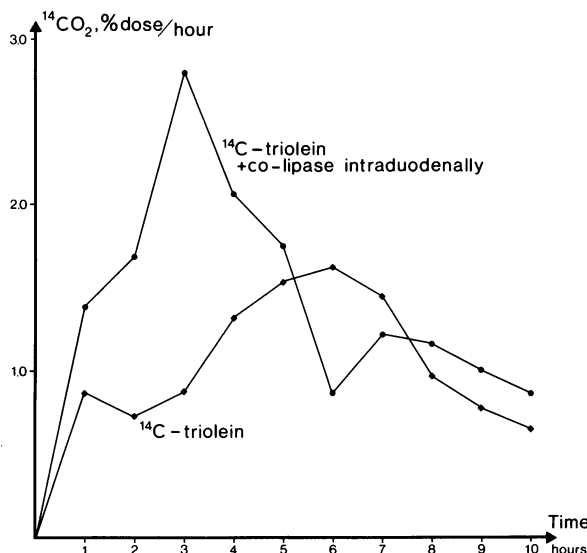


Fig. 2 Case 1. Triolein breath test with and without co-lipase infusion intraduodenally.

FAT BALANCE

Both brothers had a steatorrhoea that improved on supplementation with enteric-coated pancreatic enzymes. The older brother had a fat absorption of 49% that improved to 95% and the younger brother had a fat absorption of 52% that improved to 88% during supplementation.

Discussion

Pancreatic lipase catalyses the hydrolysis of triglycerides stepwise into monoglycerides and free fatty acids. Bile salts inhibit the action of lipase by displacement of the enzyme from the triglyceride interface. Co-lipase, which is another pancreatic protein, is capable of bind-

ing to the bile salt covered triglyceride and at the same time binding to lipase. In this way co-lipase anchors lipase to the interface of the substrate in the presence of bile salts.³ Co-lipase in itself has no lipolytic activity.³ Defective fat digestion and absorption will occur if either lipase or co-lipase activity in the small intestine is low.

In this paper the first two cases of isolated co-lipase deficiency are described in two brothers. They presented with loose stools caused by a marked steatorrhoea. The physiological importance of co-lipase was clearly demonstrated in the older brother by giving a fat meal together with purified co-lipase intraduodenally, which resulted in an improved fat absorption. It was also demonstrated that it is possible to treat co-lipase deficiency with enteric coated pancreatic enzymes, administration of which in these two brothers resulted in normal stools and almost normal fat absorption.

Isolated lipase deficiency has been described in 12 patients.⁶⁻¹³ Five of these patients have been tested for co-lipase and all had normal values.⁹⁻¹³

Patients with isolated lipase deficiency have a fat absorption of about 50% which improves on pancreatic enzymes. Thus either lipase or co-lipase deficiency results in the same pattern of fat absorption.

The finding of an isolated enzyme deficiency in two brothers combined with the consanguinity of the parents indicates a recessive inheritance. Surprisingly, our patients did not develop symptoms until the age of 5 years. This could be explained by the existence of other lipolytic activities in the gastrointestinal tract as gastric lipase and pancreatic esterase.¹¹ A late appearance of symptoms was also seen in some of the patients with isolated lipase deficiency.^{8,9,12}

The older boy has a liver cirrhosis possibly secondary to a viral hepatitis. As he has normal concentrations of bile salts in the small intestine, the liver disease should not affect his fat malabsorption. The liver disease of the

older brother and the skin infection of the younger brother are probably not related to co-lipase deficiency, as they do not occur in both boys.

Both our boys have gall stones. In patients with pancreatic insufficiency malabsorption of bile salts occurs.²⁰ The increased ratio of glycine- to taurine-conjugated bile salts in the duodenum in our patients indicates faecal loss of bile salts.²¹ A malabsorption of bile salts may cause a fall in the ratio of bile salts to cholesterol in the bile and result in precipitation of cholesterol stones.²²

The older boy had a megaloblastic anaemia due to a vitamin B12 deficiency. Defective absorption of vitamin B12 has been observed in patients with pancreatic insufficiency.²³ Co-lipase could be involved in the absorption of vitamin B12.

In Shwachman's syndrome exocrine pancreatic insufficiency is combined with bone marrow hypoplasia.²⁴ Shwachman's syndrome is excluded in these two boys, as, apart from co-lipase deficiency, all other enzymes are normal.²⁵

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