Case Report

Carnitine palmityl transferase I deficiency in a Saudi family

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ABSTRACT

Carnitine palmityl transferase I is the key enzyme in the carnitine dependent transport of long chain fatty acids across the mitochondrial inner membrane and its deficiency results in a decrease rate of fatty acids beta-oxidation with decreased energy production. We reported a family of 3 affected siblings who are the product of a first degree cousin marriage. The first 2 presented with typical Reye-like syndrome with unconsciousness, hepatomegaly, hypoglycemia, hyperammonemia and very high liver enzymes. Liver biopsy showed steatosis. On screening of the complete family, the 3rd sibling was found to have hepatomegaly. The 3 siblings showed an acyl carnitine profile with very high free carnitine with almost absent long chain acyl carnitines, suggestive of carnitine palmityl transferase I deficiency. This was confirmed by enzyme analyses in fibroblast cultures. These patients were effectively treated with a diet high in carbohydrate, low in long chain fatty acids with medium chain triglycerides. In conclusion, carnitine palmityl transferase I deficiency is an important cause of Reye-like syndrome, which may be treated easily with very good results if detected early in life.

Keywords: Carnitine palmityl transferase deficiency, hepatic, type I.

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Carntine palmityl transferase I (CPT-I) is localized in the outer mitochondrial membrane, and it catalyzes the first reaction in the transport of long chain fatty acids from the cytoplasm to the mitochondrion after the formation of their acetyl coenzyme (CoA) esters by a long chain acyl-CoA synthetase (ligase). Carnetine palmityl transferase I (CPT-I) is considered to be the rate-limiting step in beta-oxidation of fatty acids due to the unique inhibition of CPT-I by malonyl-acetyl coenzyme. The outer membrane CPT-I, the inner membrane CPT-II, together with a carnitine-acylcarnitine translocase, initiate the mitochondrial oxidation of long chain fatty acids though their sequential actions.[1,2] A defect of CPT-I would be expected to lead inadequate formation of ketone bodies in response to fasting, along with inadequate gluconeogenesis and hypoglycemia.[1] Three different clinical phenotypes of CPT (EC 2.3.1.21) deficiency are known, hepatic,[3,4] muscular[5] and hepatocardiomuscular,[6] in the hepatic form CPT-I is deficient whereas CPT-II is normal, while in the other 2 types CPT-II is deficient with normal CPT-I. Deficiency of CPT-I (OMIM 255120) was first described in1980.[3] Two different isoforms of CPT-I have been described, the hepatic (CPTIA) OMIM 600528 and the muscle (CPTIB) which are encoded by different genes, localized on $11q_{3.1\text{-}13.5}$ and $22q_{13.31\text{-}13.32}$.[7] Deficiency of CPT-I (OMIM 255120) was first described in 1980.[4] Approximately 15 cases with

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CPT-I deficiency have been reported in the literature, in this paper we reported 3 affected siblings with CPT-I deficiency in a single family.

Case Report. ***Patient 1.*** A 13-month-old girl, a product of a first degree cousin marriage. Both parents with sickle cell trait. The girl was admitted with a 3 day history of acute gastroenteritis with lethargy, found to be drowsy but well hydrated with normal growth and development. Her liver was 10 cm below the costal margin (Table 1). Her blood glucose was 0.5 mmol/L, her aspartate transaminase (AST) was 161 (U/L) (N: 2-37), her alanine aminotransferase (ALT) was 140 U/L (N: 2-40), her alkaline phosphatase was 768 U/L (N 250-850). Lactate dehydrogenase (LDH) and creatinine kinase (CK) were normal. Lactate was 1108 μm/L (N: 1100-2200), pyruvate 166μm/L (N: 20-250). Ammonia was 95 μmol/L (N: 0-50). She had mild metabolic acidosis with bicarbonate of 17 mmol/L (Table 2). Urine was negative for ketones and her urine pH was 5. The patient responded very well to glucose infusion of around 7-8 mg/kg/min. A metabolic disorder was suspected and she was promptly started on L-carnitine 100 mg/kg/day after obtaining blood and urine for metabolic studies. Her blood for tandem mass spectroscopy (MS) showed very high free carnitine of 138 and 102 μm/L (N: 8-70 μm/L) on 2 occasions with almost absent long-chain acyl carnitines (Figure 1). Her urine gas chromatography/mass spectroscopy (GC/MS) was normal with no dicarboxylic aciduria (Table 2). A diagnosis of CPT-I deficiency was suspected and the patient was started on a special diet high in carbohydrate, low in long chain fatty acids, 10% of total calories with added medium chain triglyceride (MCT) oil 1-2 g/kg/day. She was also started on riboflavin 50 mg/kg bid. The lipid profile showed cholesterol of 8.5 mmol/L (N: 0-4.8) and triglyceride of 7.79 mmol/L (N: 0.1-4) which significantly decreased within a few days to 3.2 and 3. Her liver enzymes, blood glucose and ammonia also returned to normal. Liver biopsy showed portal fibrosis with micro and macro vesicular steatosis with normal electron microscopic examination (Figure 2). The eye exam and magnetic resonance image (MRI) brain scan were normal. Echocardiogram showed no cardiomyopathy (Table 2). Her CPT-I activity in fibroblast was found to be strongly deficient with little residual activity (0.011 nmol/min/mg). Subsequent studies in fibroblasts from the whole family revealed that 2 siblings were found also to have the disease (Patients 2 and 3) (Table 3).

Patient 2. A 2 and a half year old brother of patient one. He was a known case of sickle cell anemia, ventricular septal defect, and was found on screening to have hepatomegaly (Table 1). His tandem MS showed a free carnitine of 100 μmol/L with very low long chain acyl carnitines (Figure 1), and normal urine GC/MS. He was placed on a special diet and L-carnitine. The patient was admitted one month later with acute dactylitis and bronchial asthma with decreased level of consciousness only responding to painful stimuli. His liver was 10 cm below the costal margin (Table 1). His hemoglobin was 7 gm/dl and blood sugar was 1 mmol/L. His ammonia was 221 μmol/L, AST was 221 U/L, ALT was 109 U/L, alkaline phosphatase (Alk phos) 3225 U/L. His lactate dehydrogenase (LDH) was 1097 U/L (N: 230-460). Urine ketones were negative and pH was 5-6. Blood gases were normal, blood culture and cerebro-spinal fluid (CSF) culture were all negative (Table 2). The patient had to be intubated and was placed on

Table 1 - Clinical features of the patients.

Clinical features	Patient 1	Patient 2	Patient 3
Age	13 months	2.5 years	5 years
Presentation	Gastroenteritis	On screening	On screening
Consciousness	Drowsy	Normal	Normal
Hx. of hypoglycaemia, convulsions	Yes	Yes	Yes
Growth	Normal	Normal	Normal
Development	Normal	Normal	Normal
Liver	10cm BCM	10cm BCM	8cm BCM
Neurologically	Normal	Normal	Normal
Hx. - History BCM - Below costal margin			

Table 2 - Investigations carried out.

Investigations	Patient 1	Patient 2	Patient 3
Blood Glucose mm/1	0.5	1.0	3
Bicarbonate meq/l	17	Normal	Normal
AST (2-37 U/L)	161	221	37
ALT (2-40 U/L)	140	109	35
Alkaline Phosphate (250- 850 U/L)	768	3225	781
LDH (230-460 U/L)	250	1097	ND
CK (50-190 um/L)	70	80	ND
Lactate (1100-2200 um/L)	1108	ND	ND
Pyruvate (20-250 um/L)	166	ND	ND
Ammonia (0-50 um/L)	95	221	60
Cholesterol (0-48 mm/L)	8.5	ND	2.4
Triglycerides (0.1-4 mm/L)	7.79	ND	0.26
Tandem MS - free carnitine um/L (8-70)	138/102	100	130
Tandem MS - long chain acyl carnitine	Absent	Very Low	Low
Urine GC/MS	Normal	Normal	Normal
Liver biopsy	Micro & Macrovascular Steatosis	Micro & Macrovascular Steatosis	ND
MRI Brain	Normal	ND	ND
CT Brain	ND	Low attenuation in brain stem	ND
Echocardiogram	Normal	Normal	Normal

ND - Not done; AST - aspartate transaminase; ALT - alanine aminotransferase; LDH - lactate dehydrogenase; CK - creatinine kinase; MRI - magnetic resonance image; MS - Mass spectroscopy; GC - Gas chromatography; CT - computerized tomography

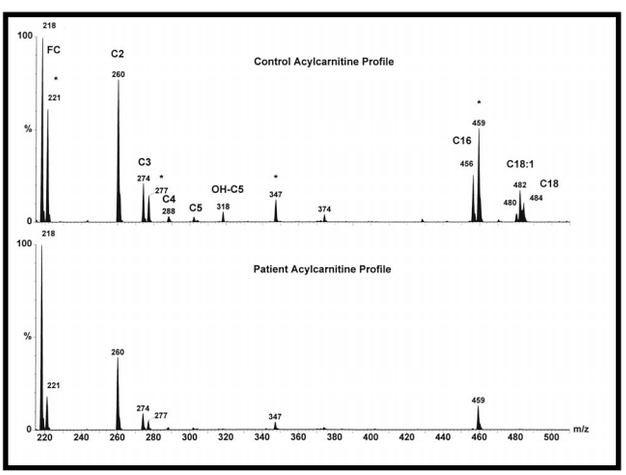

Figure 1 - Blood spot free carnitine and acyl carnitine profiles (tandem mass spectroscopy). With high free carnitine and a very low long chain acyl carnitine.

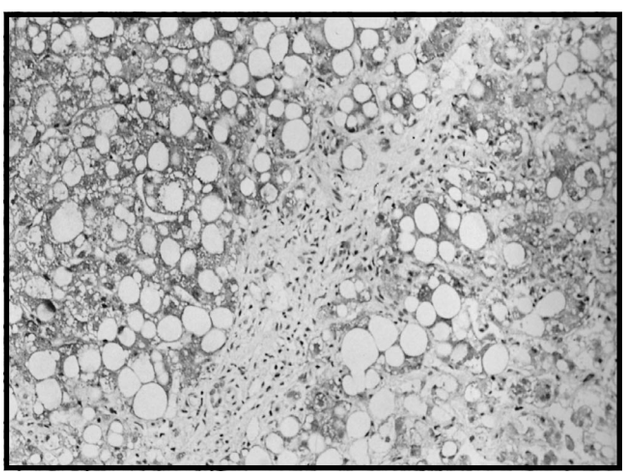

Figure 2 - Liver biopsy with periportal fibrosis, with micro and macrovesicular steatosis.

Table 3 - Carnitine palmityl CoA transferase I (CPT-I) in controls and affected family.

Affected Family and Controls	Carnitine palmityl-CoA transferase I (nmol/min/mg)
Father	0.256
Mother	0.230
Sister	0.317
Patient 1	0.011
Patient 2	0.003
Patient 3	0.005
Controls in experiment	0.58± 0.26 (N=12)
CoA - acetyl coenzyme	

glucose infusion of 8 mg/kg/min. A computerized tomography (CT) brain scan showed low attenuation in the brain stem with no increased intracranial pressure. His echocardiogram showed no cardiomyopathy. Liver biopsy showed macrovesicular steatosis with portal fibrosis, with normal electron microscopic study (Table 2). His CPT-I activity in fibroblast was 0.003 nmol/min/mg as compared to a control value of 0.306; 0.257 (Table 3). The patient responded very well to riboflavin 100 mg bid and a special diet (the same diet as his sister, patient one. He showed progressive improvement in his liver function and size, ammonia and blood glucose.

Patient 3. A 5-year-old boy, another brother of the previous 2 patients with normal growth and development. He was also found on screening to have hepatomegaly of 8 cm below the costal margin and to have acyl carnitine profile suggestive of CPTI deficiency. The patient had a history of hypoglycemia and previous convulsions (Table 1). At that time his glucose was 3 mmol/L. His AST was 37 U/L, ALT 35 U/L, Alk phos 781 U/L, triglyceride 0.26 mmol/L, and cholesterol 2.4 mmol/L. Ammonia and CK were normal (Table 2). His CPT-I activity in fibroblast was 0.005 nmol/min/mg as compared to a control values of 0.58 ± 0.26 (n=12) (Table 3). The patient was also treated with riboflavin and the same special diet as his siblings. Blood tandem MS and urine GC/MS and CPT-I activity on both parents were normal.

Discussion. Defects in energy metabolism that result in a predisposition to potentially fatal metabolic crisis predominantly involves the lipid pathway, rather than glycogenolysis or electron transport, because of the central role of lipids in the normal adjustment to caloric deprivation. Such defects include carnitine transport, CPT-II, carnitine-acylcarnitine translocase, medium chain acyl-CoA dehydrogenase and long-chain acyl-CoA dehydrogenase. Severe triglyceride accumulation as fine droplets in liver tissue, cardiac and skeletal muscle, and proximal renal tubules is a hallmark in each of these diseases.[10] Many patients with defective oxidation of long-chain fatty acids suffer acute Reye-like attacks. These resemble those, which predominate in medium-chain acyl-CoA dehydrogenase deficiency and presumably arise by similar mechanisms. Suggestions have included: (a) the decreased capacity of fatty acid catabolism to produce energy, particularly in response to fasting; (b) impaired ketone body generation exacerbating this energy deficit; (c) toxic effects of accumulating acyl-CoA intermediates or the corresponding acylcarnitines; and (d) toxicity of the increased concentrations of free fatty acids. Reye-like episodes with hypoglycemic coma and hepatic dysfunction are common in both plasma membrane carnitine transporter deficiency and hepatic CPT-I deficiency. Both these defects are located outside the mitochondrial matrix, which suggests that an energy deficit alone, without specific intramitochondrial disturbances, may be sufficient to induce such attacks.[1]

We treated our patient as in other long chain beta-oxidation defects with a special diet low in long-chain fatty acids and high in carbohydrate and MCT oil, with proven ketogenesis and absence of hyperammonemia. This points to sufficient energy being produced in these patients by oxidation of MCT, as the medium-chain fatty acids bypass the carnitine-dependent mitochondrial transport system. The limited supply of long-chain fatty acids then leads to decreased production of long-chain acyl-CoA esters and the corresponding acylcarnitines, leading in turn to improved energy production with no hyperammonemia, improved liver enzymes, efficient ketogenesis and no hypoglycemia[11] which indicates that CPT-I appears to determine the overall rate of oxidation of fatty acids in the liver.

The importance of early diagnosis and treatment of this disorder must be emphasized in these patients to prevent brain damage. Screening families and genetic counseling is important for early detection and treatment, and even for antenatal diagnosis. Blood tandem MS and urine GC/MS are such valuable rapid, low cost diagnostic tools as is true of most organic acidemias, aminoacidemias and fatty acid oxidation defects.

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