Carnitine-acylcarnitine translocase deficiency

Clinical course of three Saudi children with a severe phenotype

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ABSTRACT

يعد مرض نقص إنزيم الكارنيتين أسيلكرنيتين ترانسلوكاز (carnitine–AcylcarnitineTranslocase) والذي اكتشفه الطبيب (McKusick 212138) اضطراباً نادراً يهدد الحياة، ويتصف بنقص سكر الدم المصحوب بانخفاض كيتونات الدم بالإضافة إلى فرط أمونيا الدم ، واعتلال كلاً من الدماغ والقلب والكبد والعضلات. ونستعرض هنا بالتفصيل الإجراءات السريرية المتبعة مع ثلاثة أشقاء سعوديين يعانون من نمط ظاهري شديد الأعراض لهذا المرض. سوف نعطي أيضاً المعلومات الحيوية الكيميائية والسريرية الخاصة بالمرضى الثلاث، وقد شرحت حالة الشقيق الثالث بالتفصيل. لقد أدى التدخل الطبي المبكر الذي شمل إعطاء المريض 25% من الدكستروز عبر الوريد ومكملات الكارنيتين ثم التدرج في تقديم حليب اصطناعي خاص قليل الدسم وغني بالكربوهيدرات إلى استجابة جيدة للعلاج وذلك من الناحية السريرية والحيوية الكيميائية. إلا أن هذا لم يمنع إصابة المريض بالتكلس الكلوي المبكر ونقص حاد في التوتو العضلي (hypotonia) وبالتالي إصابته بخلل في الأوعية الدماغية. توفي المريض بعمر 18 شهراً نتيجة لانهيار تعويض التمثيل الغذائي، وهذا يدل على أن مرض نقص إنزيم الكارنيتين أسيلكرنيتين ترانسلوكاز ما زال يعد اضطراباً مميتاً بالرغم من التدخل الطبي المبكر والمكثف.

Carnitine-acylcarnitine translocase (CACT) deficiency (McKusick 212138) is a rare life threatening disorder characterized by hypoketotic hypoglycemia, hyperammonemia, encephalopathy, cardiomyopathy hepatopathy, and myopathy. Here, we present a detailed clinical course of 3 Saudi siblings with a severe phenotype. The third patient was described in more detail. Early medical intervention in the form of 25% dextrose intravenous infusion and carnitine supplement followed by a gradual introduction of a high carbohydrate low fat special formula resulted in a good clinical and biochemical response to the treatment in our patient. However, early nephrocalcinosis, severe hypotonia, and subsequently intravascular cerebral accident could not be prevented. He died at 18 months of age as a result of metabolic decompensation. This suggests that CACT deficiency is still a lethal disorder even with an early and aggressive medical intervention.

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Carnitine-acylcarnitine-translocase (CACT) is an inner mitochondrial membrane protein that is necessary for the transport of long-chain fatty acids into the mitochondrial matrix, transferring the acylcarnitines esters across the mitochondrial membrane in exchange for free carnitine. Deficiency of the CACT (McKusick 212138) is a rare and a life threatening fatty acid oxidation disorder. It is characterized by a neonatal onset of hypoketotic hypoglycemia, hyperammonemia, encephalopathy, cardiomyopathy, hepatopathy, and myopathy. Only few patients have been reported with a late and mild presentation. Most of the reported cases so far died within the first 3 years of life.[1] Recently, a favorable outcome in a severely affected patients with CACT deficiency treated with medium chain triglycerides (MCT) rich diet and carnitine was reported.[2] Here, we report 3 affected siblings with a severe phenotype. The index case was described in a more detail. Aggressive and immediate medical intervention had significantly altered the natural history of the disease. However, CACT deficiency has remained a lethal disorder with a high risk of morbidity and mortality.

Case Report. The proband was the sixth child born at 37 weeks gestation by a normal vaginal delivery to a

healthy distantly related Saudi Arab couple following a non-eventful pregnancy. He had 3 living healthy and 2 deceased siblings. The records for the first and the second deceased siblings were reviewed. The first one was a full term baby boy who had unexplained cardiorespiratory arrest at 3-days of age with severe hypoglycemia and mild elevation of liver enzymes. Metabolic work up revealed abnormal urine organic acids with increased dicarboxylic acids (C6-10) and tyrosine metabolites, low serum carnitines. The plasma acylcarnitines profile showed a pronounced elevation of long-chain (C12-C18). Liver biopsy showed hepatic steatosis. The patient died of repeat cardiorespiratory arrest at 45 days of age. The second deceased child was a baby girl born at 37 weeks gestation. She required hemodialysis for severe hyperammonemia on the second day of her life; serum ammonia level was 1192 umol/L (0-45). Echocardiogram showed myocardial hypertrophy with decreased function. The basic metabolic work up including urine for organic acids, serum carnitines and plasma acylcarnitines profiles resembled the first sibling. Cultured skin fibroblasts were unsuccessful. The proband developed poor feeding on the second day of his life. Soon, he became severely lethargic with a poor peripheral perfusion. The patient was immediately started on D25W intravenous fluid and insulin infusion along with L-carnitine 100mg/kg/day. Within 24 hours of this medical intervention, he had remarkable clinical improvement. In addition his serum ammonium, lactic acid, and CK levels normalized. Two days later, he was started on total parental nutrition (TPN) excluding the intralipid. Subsequently, a special formula through nasogastic tube was introduced gradually on him. The feed was modified to provide a total of 120 calorie/kg/day. This was fractionated into 80% carbohydrate, 10% protein and 10% fat (50% as MCT). At 4 weeks of age, the baby is able to get fed orally every 3 hours. Apart from a mild hypotonia, his clinical assessment was normal. The findings of his initial investigations showed a serum ammonia level of 139 µmol/L, blood sugar 66 mg/dL, lactic acid 3.0 mEql/L and CK 990 IU/L, increased C6-C10 dicarboxylic acids excretion in the urine. The plasma acylcarnitines profile showed elevation of various chains particularly C16, C1:16, C1:18, and C2:18. Fatty acid oxidation probe assay on cultured skin fibroblasts performed at Mayo Clinic showed a significant elevation of saturated and unsaturated C16-C18 species. Palmitc and myristic acids oxidation study was carried out at Metabolic Disease Laboratory, Children Medical Center, Dallas, Texas. The activity for Palmitic acid was 0. 81±1.15 units pmol/min/mg protein and 1.59±0.4units pmol/min/mg protein for myristic acid (control; 47.24±19.34, and 37.35±9.25). Carnitine palmityol transferase (CPT II) activity was normal. The measured activity for CACT on the patients's cultured fibroblasts was 0.06 nmol/min/mg protein. The control was 1.89 nmol/min/mg protein and the normal range 1.36±0.32 (0.90-1.90). This was consistent with a severe enzyme deficiency. At 4 months of age, the patient was thriving well on the same special formula along with L-carnitine supplement. His weight was 6.14 kg (25-50%), length 61 cm (10-25%) and head circumference 39 cm (2%). His development was normal for his chronological age despite being mildly hypotonic. At the same time, he had to be admitted to the hospital with an acute metabolic decompensation following an episode of a mild gastroenteritis. The blood urea nitrogen peaked to 16 mg/dL and creatinine 3.2 mg/dL. Renal ultrasound showed bilateral medullary nephrocalcinosis with suspected stone formation (**Figure 1**). Twenty hours urine collection showed a total calcium excretion was 14 mg/kg/day (normal value <4 mg/kg/day), protein, tubular phosphorus reabsorption, and uric acid excretion were within the normal ranges. Following this episode, the patient noticed to be more hypotonic and was unable to feed orally. At one year of age, he developed right sided weakness. The brain MRI showed an acute infarct involving the left middle cerebral artery territory (**Figure 2**), and magnetic resonance angiogram (MRA) confirmed a marked attenuation of the left middle cerebral artery consistent with intravascular occlusion (**Figure 3**). Extensive coagulation study including prothrombin time (PT), partial thromboplastin time (PTT), antithrombin 3, factor V, protein S antigen, and protein C were normal. Antinuclear antibody (ANA) and homocysteine blood level were normal. Subsequently, the patient had an acute bronchiolitis secondary to respiratory syncytial virus (RSV) infection that led to a progressive respiratory insufficiency and then respiratory failure requiring ventilation. Several trials of extubation were unsuccessful and thereby he underwent a tracheostomy. A follow up echocardiogram at 16 month of age showed mild biventricular hypertrophy with dilatation with the left ventricle systolic ejection fraction down to 24%. He died at 18 month of cardiac arrest during one acute metabolic decompensation.

Discussion. Carnitine-Acylcarnitine-Translocase deficiency is considered the most lethal disorder of the carnitine cycle. The 3 siblings described here presented at birth with similar clinical manifestation highly suggestive of long chain fatty acid oxidation disorders. These included encephalopathy, hypertrophic

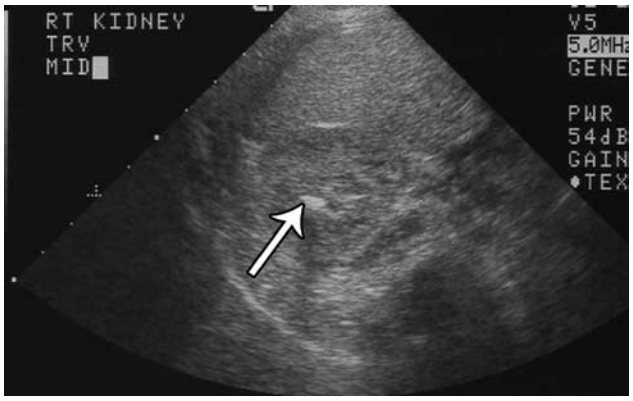

Figure 1 - Renal illustrating the medullary nephrocalcinosis (arrow).

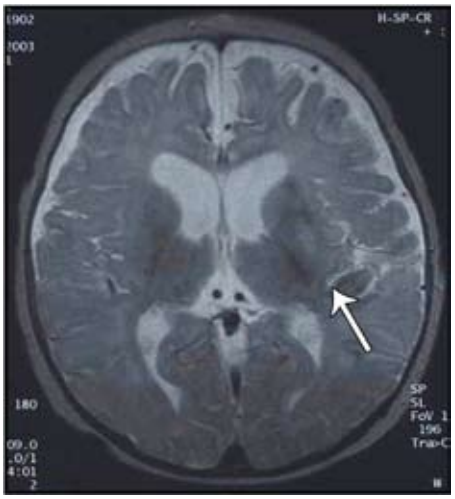

Figure 2 - Brain MRI-T2 image which showed a hyperintense signal involving the left tempro-parietal area with caudate and putamin nuclei (arrow).

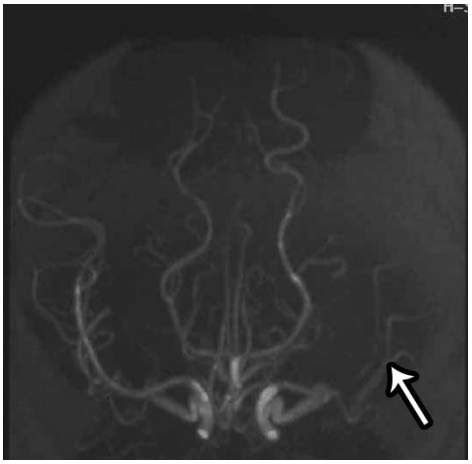

Figure 3 - Brain MRA showing marked attenuation of the left middle cerebral artery (arrow).

cardiomyopathy, hepatopathy and, hypoglycemia.[3-5] The hyperammonemia was severe enough in the second affected sibling to require hemodialysis. The plasma acylcarnitines profile was consistent in the 3 siblings and showed elevation of long chains in particularly saturated and unsaturated C16-C18. This profile is typically seen in long chain fatty acids oxidation disorders secondary to either CPTII or CACT deficiencies. The enzyme study conducted on the cultured skin fibroblasts of the index case confirmed the presence of a normal CPTII activity and severe deficiency of CACT. Unfortunately, we were unable to conduct genetic study on him. In addition to the presence of the above described typical biochemical abnormalities, our index patient developed hypokalemia, hypophosphatemia, hypocalcemia in addition to the metabolic acidosis during his metabolic crisis. Twenty hours urine collection for calcium excretion confirmed the presence of hypercalciuria, and renal ultrasound showed bilateral nephrocalcinosis. The electrolytes disturbance was observed during the acute metabolic crisis improved dramatically following high concentration of dextrose infusion. This supports the hypothesis of the energy production defect during this time. The patient's course was also complicated with an acute cerebral infarct secondary to occlusion of the left middle cerebral artery. A co-existing disorder such as coagulopathy, and vasculitis was ruled out on him. Stroke is a well known systemic complication of different type of inborn errors of metabolism and can be a presenting manifestation. It is generally agreed that the principle of treating any fatty acid oxidation disorder is inhibition of tissue lipolysis. This has been established by avoidance of prolonged fasting and providing a high calorie diet rich in carbohydrate. A high concentration of dextrose D20-25% in conjunction with insulin infusion has been suggested in order to overcome the metabolic crisis of CACT deficiency during neonatal period. More recently, the use of MCT oil with a different proportion of fat (1% of C6, 62.3% of C8, 23% of C10, and 0.4 and of C12) and carnitine was found to be very effective in reducing the concentration of abnormal acylcarnitines and increasing the level of acetylcarnitine. Carnitine is essential for removal of the toxic acyl moieties via conjugation to form acylcarnitines, which are subsequently eliminated through the kidneys and the bile system. This mechanism will help to restore the concentration of CoA in the body. Long chain acylcarnitines have been suggested to be cardiotoxic and provoke arrhythmia. However, carnitine supplementation is still considered a major factor for fatty acid oxidation disorders therapy and may be protective against the toxic effect of free fatty

acids on the cardiac tissues (Iacobazzi et al, 2004).[1] We had confirmed a dramatic improvement in clinical and biochemical status within 24 hours of initiating this regimen of treatment. We were successful in maintaining a good metabolic control in our patient for the first four month of his life. We believe that aggressive and urgent medical intervention may significantly alter the course of this severe type of fatty acid oxidation disorder. However, CACT deficiency remains a lethal disorder with an increased risk of cardiomyopathy and sudden death. With increased rate of survival, more systemic dysfunction will be encountered. The families need to be counseled extensively on the extent and nature of complication and often lethal outcome despite aggressive intervention as was seen in our case.

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