

## Primary Systemic Carnitine Deficiency Presenting as Recurrent Reye-Like Syndrome and Dilated Cardiomyopathy

Jia-Woei Hou, MD, PhD

Carnitine deficiency syndrome is a rare and potentially fatal but treatable metabolic disorder. I present a 6-year-old girl with primary systemic carnitine deficiency (SCD) proved by very low plasma carnitine level. Her major clinical features included neonatal metabolic acidosis, epilepsy, recurrent infections, acute encephalopathy, and dilated cardiomyopathy with heart failure before 4 years of age. Other features such as hepatomegaly, hypoglycemia, or hyperammonemia were noted around 5 years of age. Her health improved with resolving cardiomyopathy after the use of L-carnitine (50-100 mg/kg/day). Patients with SCD have high morbidity and mortality. If SCD is suggested as a cause of Reye-like syndrome or dilated cardiomyopathy, L-carnitine therapy should be initiated as a diagnostic test immediately, until the definite diagnosis is confirmed. (*Chang Gung Med J* 2002;25:832-7)

**Key words:** carnitine, Reye's syndrome, cardiomyopathy.

During infancy or early childhood, patients with underlying metabolic diseases may present with acute metabolic disturbance simulating Reye's syndrome (RS). Just as several forms of inherited organic acidemias and fatty acid oxidation disorders, patients with primary systemic carnitine deficiency (SCD), although rare, can also present with features like RS.<sup>(1,2)</sup> L-Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) is a quaternary amine which can either be biosynthesized from its endogenous precursors, lysine and methionine, or be exogenously derived from nutrient intake.<sup>(3)</sup> L-Carnitine plays a critical role in fatty acid metabolism because it facilitates the transport of long-chain fatty acids (LCFA), as acyl coenzyme A esters, across the mitochondrial membrane, and is thus an essential component of normal fatty acid  $\beta$ -oxidation in the mitochondrial matrix.<sup>(3)</sup> Carnitine deficiency syndrome may occur when intracellular free carnitine is not sufficient to accomplish the primary functions of carnitine. I pre-

sent a girl with primary SCD with recurrent Reye-like syndrome and dilated cardiomyopathy. The diagnosis of primary SCD was confirmed after extensive metabolic studies, including urine organic acid profile and plasma carnitine level.

### CASE REPORT

A 6-year-old girl was admitted due to conscious disturbance with convulsions. On initial examination at the emergency department, she breathed rapidly (46/min) and deeply. Recent history of cold sweats, abdominal pain and common colds were also noted. Intravenous infusion with glucose solution was given due to an earlier blood glucose level of 7 mg/dL. Her vital signs became stable and her consciousness recovered gradually (from E<sub>2</sub>V<sub>2</sub>M<sub>5</sub> to E<sub>4</sub>V<sub>5</sub>M<sub>5</sub>). She is the second child of healthy, non-consanguineous parents. No perinatal insult, history of head trauma, or drug exposure was noted.

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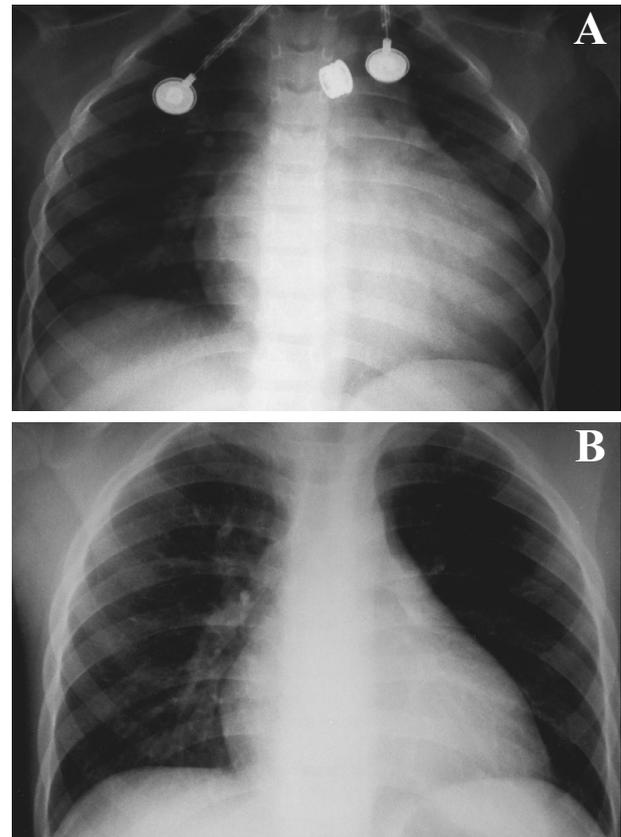
From the Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan

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Address for reprints: Dr. Jia-Woei Hou, Division of Medical Genetics, Department of Pediatrics, Chang Gung Children's Hospital, 5-7, Fu-Shin Street, Kweishan, Taoyuan 333, Taiwan, R.O.C. Tel: 886-3-3281200 ext.8203; Fax: 886-3-3278283

However, she was previously hospitalized 8 times due to the following: (1) neonatal fever and metabolic acidosis of unknown cause at 11 days old; (2) drowsiness and seizure with normal biochemical and microbiological results at 2.1 years old; (3) pneumonia, urinary tract infection, drowsiness, and dilated cardiomyopathy at 2.3 years old, when digitalis and captopril were used; (4-6) respiratory tract infections, cardiomyopathy, drowsiness, and epilepsy at 2.5, 2.8 and 3.1 years old, respectively; and (7,8) sepsis or pneumonia, drowsiness, and heart failure at 4.9 and 5.7 years old, respectively.

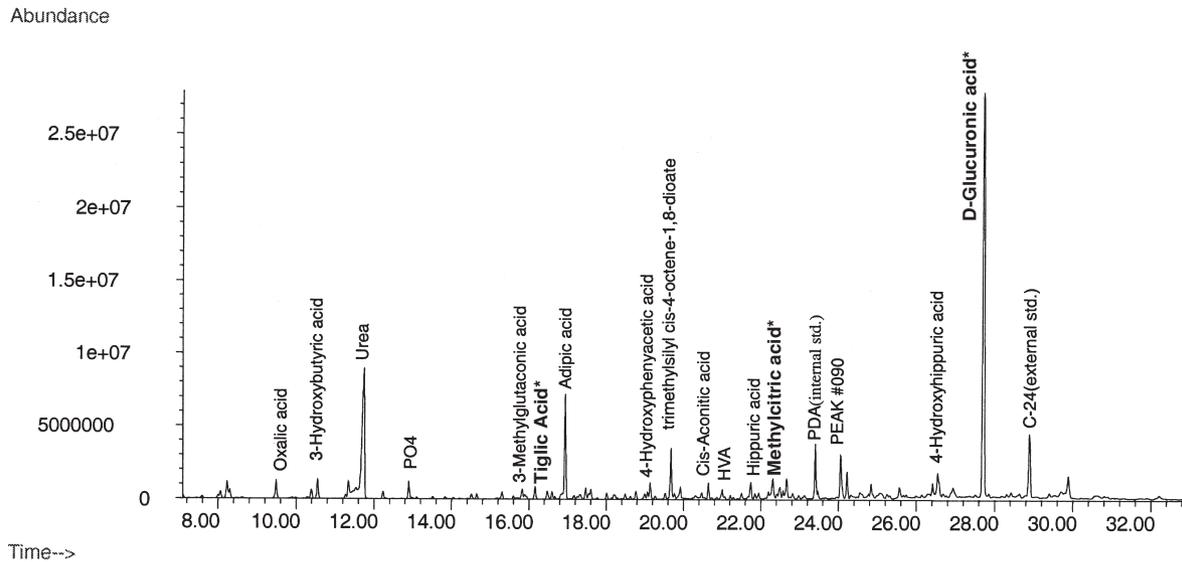
The patient looked thin and short (body weight, 13.5 kg; body height, 101 cm) without jaundice. No apparent craniofacial dysmorphism were found. Her breathing sounds were clear and there was no heart murmur. The liver was palpable 6 cm below the right costal margin. No specific odor was smelled from her urine or breath. The muscle power and reflexes were all within reference ranges. The chest films showed marked cardiomegaly with cardio-thoracic ratio of 80% (Fig. 1A). The plain abdomen films showed no abnormalities. Laboratory results showed elevated levels of serum aspartate aminotransferase, 75 U/L; alanine aminotransferase, 45 U/L; ammonia (NH<sub>3</sub>), 391 µg/dL; urea nitrogen, 36 mg/dL; creatine kinase (CK), 302 U/L (15-130) with CK-MB: 73 (normal < 16); and normal serum levels of bilirubin, sodium, potassium, calcium, creatinine, and chloride. Hemogram showed a hemoglobin level of 11.6 g/dL, a leukocyte count of 17200/mm<sup>3</sup> (70% segmented, 4.5% banded, 7% monocytes, 17.5% lymphocytes, and 1% atypical lymphocytes) and normal platelet count. The serum level of C-reactive protein was 6.3 mg/L. Urinalysis revealed only trace ketones. Cerebrospinal fluid (CSF) examination results were negative. The blood gas was pH of 7.390, PCO<sub>2</sub> of 26.3 mmHg, PO<sub>2</sub> of 149.7 mmHg, HCO<sub>3</sub> of 15.9 mEq/L, and base excess of -7.4 mEq/L (under 30% oxygen) with increased anion gap (23 mEq/L). The levels of lactate/pyruvate were 8.0/0.85 mg/dL, and her plasma amino acid pattern was normal. The results of microbiological studies of urine, blood, and CSF were all negative. The computed tomographic scan of the head showed mild brain edema. Electrocardiography showed left ventricular hypertrophy and echocardiogram revealed dilated cardiomyopathy with ejection fraction (EF) of 31%. The plasma carnitine level (free form/total)



**Fig. 1** (A) Chest radiography of the patient presents with cardiac failure due to dilated cardiomyopathy. (B) Following 3 months of oral L-carnitine supplementation, a subsequent radiography reveals resolution of cardiomegaly.

was below 5/5 µmol/L (reference range, 27-49/ 36-58 µmol/L). The urine gas chromatography/mass spectrometry (GC/MS) study for organic acids profile showed mildly increased adipic, methylcitric, and d-glucuronic acids (Fig. 2). The diagnosis of primary systemic carnitine deficiency, complicated with epilepsy, hypoglycemia, dilated cardiomyopathy, Reye-like syndrome, failure to thrive, and short stature was established. After treatment with oral L-carnitine (50 mg/kg/day) for 3 months, she was much improved clinically with carnitine level of 22.5/32.5 µmol/L. Sequential chest radiographs demonstrated decreased cardiomegaly (Fig. 1B), and the echocardiographic studies documented increases in the EF (61%) and reduction of the end diastolic volume. At the 9<sup>th</sup> month of treatment, the dosage was raised to 100 mg/kg/day due to relatively low

## CHROMATOGRAM:



**Fig. 2** Urine organic acid analysis by GC/MS study showing mildly increased dicarboxylic acid (i.e., adipic acid), and methylcitric acid.

levels of carnitine (9.93/14.56). No more hypoglycemia, hyperammonemia, or conscious disturbance occurred. Her appetite became better with appropriate weight gain and growth. The carnitine levels in her mother and father were 18.53/22.76  $\mu\text{mol/L}$  and 15.15/23.56  $\mu\text{mol/L}$ , respectively.

## DISCUSSION

Reye's syndrome is an acute noninflammatory encephalopathy associated with evidence of hepatic dysfunction. It has been noted to be associated with the use of aspirin following various viral infections, and numerous other disease states including liver necrosis, drug intoxication and several inherited metabolic diseases (IMD) which may produce symptoms and signs mimicking RS.<sup>(1,2)</sup> The diagnosis of SCD is difficult. In this case, the initial features including epilepsy and dilated cardiomyopathy did not show specific clues to alert the doctors. Finally, according to her complicated medical history and after extensive metabolic studies (urine GC/MS, plasma amino acids, and carnitine levels), a certain IMD such as SCD was highly possible. The clinical course of this patient was consistent with the diagno-

sis of primary SCD including features similar to RS (encephalopathy, elevation of serum transaminase values, hypoglycemia and hyperammonemia), dilated cardiomyopathy, very low concentrations of free and total carnitine in plasma, and an excellent response to carnitine therapy. Other metabolic etiologies that may lead to RS (urea cycle defects, and organic acidurias) or RS/ cardiomyopathy (fatty acid oxidation disorders, respiratory chain disorders, and glycogenosis) were excluded using the laboratory findings.<sup>(1,2)</sup>

Carnitine is synthesized from lysine and methionine, however, the greater part is derived from the diet.<sup>(3)</sup> Cellular carnitine acts as an obligatory cofactor for  $\beta$ -oxidation of fatty acid by facilitating the transport of LCFA across the mitochondrial inner membrane as acylcarnitine-esters and also modulates the intramitochondrial Coenzyme A (CoA)/acyl-CoA ratio.<sup>(4)</sup> Impairment of LCFA transport into the mitochondria results in failure of energy production and accumulation of triglycerides in tissues dependent on oxidative metabolism, such as skeletal and cardiac muscle.<sup>(3,4)</sup> Failure to modulate the CoA/acyl-CoA ratio also impairs energy production and allows the accumulation of toxic acyl-CoA compounds.

These aberrations in the metabolism may cause a variety of potentially fatal symptom complexes during infancy and childhood, including neonatal death, hepatic encephalopathy, dilated cardiomyopathy and progressive skeletal myopathy.<sup>(3,4)</sup> In addition, the accumulation of toxic fatty acyl derivatives impedes gluconeogenesis and urea cycle function and, in turn, causes hypoketotic hypoglycemia, elevations in transaminase, and hyperammonemia.<sup>(1,4)</sup>

Primary systemic carnitine deficiency is an autosomal recessive disorder. Two different clinical presentations have been described.<sup>(3)</sup> Some young patients (< 2 years of age) may first have episodes of fasting hypoketotic hypoglycemia or a Reye-like syndrome, but the majority of patients are diagnosed later in their childhood when progressive cardiomyopathy with or without skeletal muscle weakness developed. In some patients, endocardial fibroelastosis also occurred. Several sudden and unexpected deaths have been reported.<sup>(5)</sup> Clinical detection is often possible when significant symptoms diagnostic of SCD are accompanied by extremely reduced carnitine levels in plasma and muscles to 1-2% of normal. Heterozygote parents may have plasma carnitine levels below the reference range (The parents had approximately 50% of normal in this report). Acute crises produced by carnitine deficiency are treated with generous intravenous glucose supplementation to correct or prevent hypoglycemia.<sup>(1)</sup> When hyperammonemia is present, protein intake must be restricted. Fluid deficits and acid/base abnormalities must be corrected. Avoidance of fasting, supplying frequent meals of high-carbohydrate content and low-fat diet are advisable in all patients with SCD. Maintenance therapy with L-carnitine 100 mg/kg daily is suggested. Cardiomyopathy often responds well to carnitine supplementation.<sup>(3,4)</sup>

There is an active transporter system across membranes in the small intestine, renal tubules, skeletal muscle, and skin fibroblasts.<sup>(6,7)</sup> In membrane-physiological studies, researchers have discovered a defect in the carnitine transporter system of the plasma membrane in SCD patients. The carnitine transporter defects impair the uptake of carnitine in the kidney, heart, muscle, and skin fibroblasts but not in the liver.<sup>(6,7)</sup> Because of the failure of muscle uptake and renal conservation of carnitine, affected patients cannot maintain adequate plasma and tissue

levels of carnitine, leading to impairment of mitochondrial fatty acid oxidation. Fasting ketogenesis may be normal, because the liver carnitine transporter is normal, but may be impaired if dietary carnitine intake is interrupted.<sup>(6-8)</sup> The fasting urinary organic acid profile may show hypoketotic dicarboxylic aciduria if hepatic fatty acids oxidation is impaired, but is otherwise unremarkable. Oxidation of accumulated fatty acid through an alternative pathway,  $\omega$ -oxidation, produces dicarboxylic aciduria.<sup>(3,4)</sup>

Systemic carnitine deficiency is the only genetic defect in which carnitine deficiency is the cause, rather than the consequence, of impaired fatty acid oxidation. Its genetic defect is in a sodium ion-dependent carnitine transporter that has been mapped at 5q31.1.<sup>(9)</sup> This transporter protein, termed OCTN2, is responsible for maintaining intracellular carnitine 20~50-fold higher than plasma concentrations and for renal conservation of carnitine.<sup>(8,9)</sup> OCTN2 has the ability to transport carnitine in a sodium-gradient dependent manner. Biochemical analysis revealed that this mutation abrogates carnitine transport. The mutation studies (homozygous deletion, compound heterozygote, and homozygous splice-site mutations) have shown evidence that loss of OCTN2 function causes SCD.<sup>(8,9)</sup>

Reye-like IMDs may result in early neonatal death with the misdiagnosis of neonatal sepsis. In the cases of positive family history of RS, unexplained encephalopathy, sudden infant death, recurrent encephalopathy or metabolic acidosis since a young age, early sampling of the body fluid or tissue is recommended to elucidate the underlying IMDs.<sup>(1,2)</sup> This would help prevent the recurrence of symptoms using diet control and medications, and help with genetic counseling. I presented carnitine deficiency syndrome, which is one of the many rare but treatable disorders, in a 6-year-old girl. It is necessary to detect and treat this disease early to decrease the morbidity and mortality rates.

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# 以反覆類雷氏症發作及擴張型心肌病變表現之原發型系統性肉鹼缺乏症

侯家瑋

原發型肉鹼缺乏症是極罕見的先天代謝疾病。一名六歲女童在住院九次後才被診斷出罹患這種疾病，病人主要的症狀包括新生兒期的代謝性酸血症，四歲以前陸續出現抽搐、重覆感染、急性腦症及擴張型心肌病變。五歲以後又出現肝腫大、低血糖症及高血氨症。經過口服L型肉鹼治療(劑量50至100 mg/kg/天)，一年半以來不再有類似症狀，心臟功能也恢復正常。缺少肉鹼有致死的可能，但若能及早發現，仍是可以治療的。當幼兒出現類似雷氏症的症狀時，肉鹼缺乏症是必須考慮的疾病之一，應及早給予L型肉鹼治療。(長庚醫誌 2002;25:832-7)

**關鍵字：**肉鹼，雷氏症，心肌病變。