Mitochondrial Fatty Acid Oxidation Disorders In Thai Infants : A Report of 3 Cases†

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Abstract

Three infants with documented mitochondrial fatty acid oxidation disorders are described in this report. **Case 1. Carnitine/acylcarnitine translocase deficiency. (CACT)** (OMIM 212138) A two-day-old male developed sudden cardiac arrest 48 hours postpartum, with a previous history of early death (day 2) in siblings with a history of parental consanguinity; somnolence, inactivity, refusal to suck within 24 h, hepatomegaly, persistent hypoglycemia, hypocalcemia, hyperkalemia and severe metabolic acidosis prior to cardiac arrest. Dried blood spots by tandem mass spectrometry demonstrated 10 x elevation of palmitoylcarnitine, moderate elevation of oleylcarnitine, steroylcarnitine and myristoylcarnitine. **Case 2. Medium chain acyl CoA dehydrogenase (MCAD) deficiency.** (OMIM 212139) A six-week-old male infant, developed sudden cardiac arrest after contacting a viral illness, resuscitated successfully in the first episode, only to succumb during the second episode, 2 weeks apart. Plasma acylcarnitine *via* tandem mass spectrometry was reported normal; however, urine organic acids *via* gas liquid chromatography and mass spectrometry demonstrated characteristic metabolites consistent with MCADD. **Case 3. Carnitine deficiency, systemic primary. (CDSP)** (OMIM 212140) A one-year-old girl with progressive dyspnea since birth and a history of parental consanguinity. Severe dilated cardiomyopathy with episodes of cardiac decompensations, hepatomegaly, anemia, generalized hypotonia, but no hypoglycemia were demonstrated prior to cardiac arrest. Extremely low carnitine level noted in dried blood spots *via* tandem mass spectrometry.

Key word : Mitochondrial Fatty Acid Oxidation Disorders, Sudden Cardiac Arrest, Cardiomyopathy

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The studies of inherited metabolic disorders (IEM) at the Division of Medical Genetics Unit, Department of Pediatrics, Siriraj Hospital Faculty of Medicine, Mahidol University was started in 1987 using limited resources available and collaboration with other expert laboratories, both in Japan and the United States. From July 1993 to March 1998 the authors collaborated with MaGee's Women and Children's Hospital of Pittsburgh and NeoGen Screen, USA using tandem mass spectrometry to diagnose high-risk infants and children for IEM from dried blood spots. In April 1998 the authors started to collaborate with Matsumoto Institute of Life Science and Kanazawa Medical University, Japan using urine filter paper and gas liquid chromatography and mass spectrometry and we have since successfully discovered several patients with metabolic disorders.

Mitochondrial oxidation of fatty acids is an essential energy producing pathway, especially during periods of fasting. The most common presentation is an acute attack of life-threatening coma and episodic hypoketotic hypoglycemia provoked by fasting and beginning in the first 2 years of life[1]. MCAD deficiency is the most common of the fatty acid oxidation disorders[2,3], may present as sudden unexplained death, sudden infant death syndrome (SIDS), Reye's syndrome or encephalopathy with or without hypoglycemia[1]. Carnitine deficiency is usually due to carnitine transport defect which responds dramatically to carnitine treatment. Avoidance of fasting, carnitine supplementation and prompt intravenous glucose therapy during acute illness all constitute effective therapy[4,5,9].

The pathway of mitochondrial β-oxidation in mitochondria plays a major role in energy production, especially during periods of fasting. The pathway is complex and includes as many as 20 individual steps[1]. The first well-documented disorders were described in the early 1970's and altogether, 12 disorders affecting mitochondrial fatty acid oxidation and ketogenesis have been defined. Fatty acid oxidation disorders may have escaped attention, in part because the pathway does not play a major role in energy production under nonfasting conditions. Thus, defects in fatty acid oxidation may be clinically silent until relatively late in fasting. Another factor contributing to the delay in their recognition is that routine laboratory tests other than qualitative urinary ketone analysis, often do not provide clues about potential defects in the fatty acid oxidation pathway. Methods to identify abnormal metabolites of fatty acids using gas chromatography coupled with mass spectrometry (GC/MS) have been available only since the mid-1970's, and has permitted the identification of patients with fatty acid oxidation defects[1].

MATERIAL AND METHOD

Case report 1 : Carnitine/acylcarnitine translocase deficiency. (OMIM 212138) (N.T.) A two-day-old, 3,400 g male infant, born to a 30-year-old mother after an uneventful pregnancy and delivery; he was breast fed and developed somnolence, inactivity and later refusal to suck within 24 hours after birth. On day 2, he became cyanotic and developed sudden cardiac arrest with persistent hypoglycemia, convulsions, and severe metabolic acidosis. There was a history of parental consanguinity (Fig. 1.) and similar episodes of cardiac arrests in two other siblings. Physical examination was normal except for respiratory distress, cyanosis, tachypnea and hepatomegaly. Hemoglobin was 11.5 g/dl, hematocrit 34.5 per cent, white blood cells 11,900/mm^3 with normal differential and platelets. Blood chemistry values were normal except blood urea nitrogen 37 mg/dl, calcium 3.8 mg/dl, bicarbonate 13 mmol/L and plasma ammonia 195 Umol/L. The venous blood pH was 7.09 and there was a wide anion gap of 22 and 37. Trace urine ketone was present. Quantitative plasma amino acids were normal except slightly elevated glutamine, proline, glycine, alanine and lysine. Urine organic acid demonstrated increased excretion of lactate, 2-hydroxybutyrate, glucose, and glycerol. Dried blood spots for tandem mass spectrometry (Fig. 2.) demonstrated 10-fold increased in palmitoylcarnitine (C16), moderate elevation of oleylcarnitine (C18:1), steroylcarnitine (C18), myristoylcarnitine (C14). Initially long-chain acyl-CoA dehydrogenase (LCAD) deficiency or very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency were considered. Subsequent consultation and confirmation with Donald Chace at Duke University Medical Center for second opinion revealed absence of C14 : 1 in the specimen making LCAD or VLCAD somewhat less likely. The possibility of carnitine/acylcarnitine translocase deficiency was finally considered. The pattern was definitely abnor-

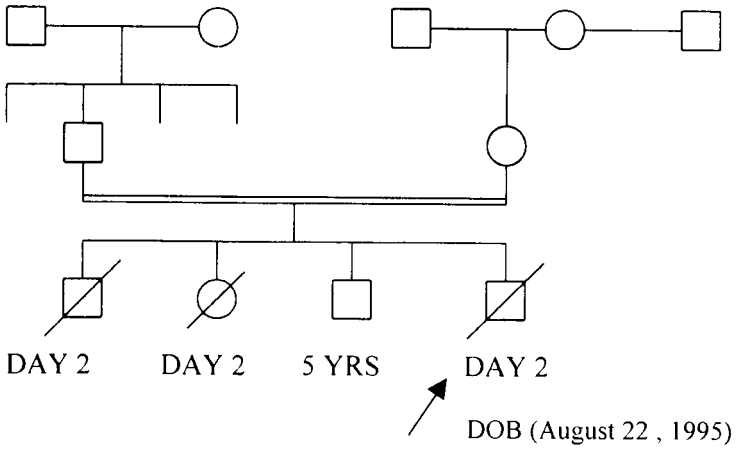

Fig. 1. History of parental consanguinity and previous deaths at 48 hours in two other siblings.

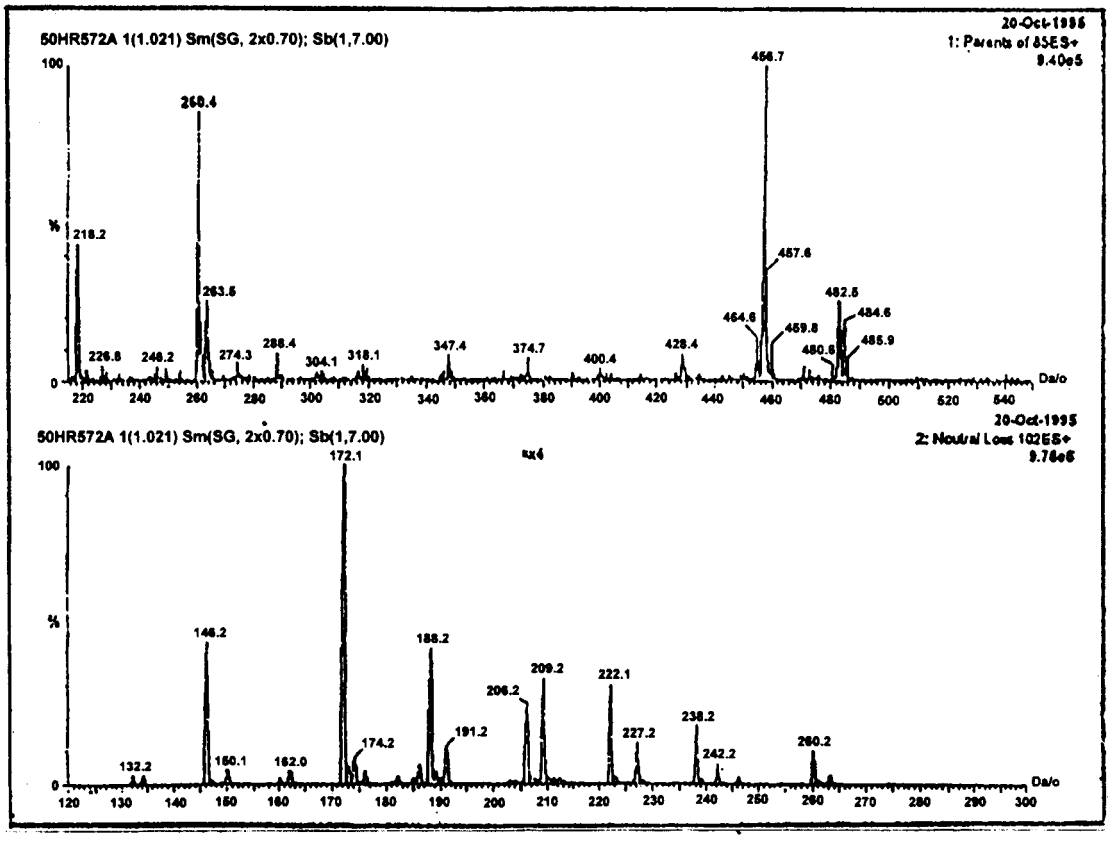

Fig. 2. Demonstrates elevation of acylcarnitine profile.

mal and involved the long-chain acylcarnitines. Autopsy findings demonstrated lipid deposition in the liver and cardiac muscle.

Case Report 2 : Medium chain acyl CoA dehydrogenase (MCAD) deficiency. (OMIM 212139) (S.N.) A six-week-old male infant, born at term, birth weight 3,460 g, after an uneventful pregnancy and neonatal course; he was the second child to unrelated parents (Fig. 3). He was formula-fed without any difficulty and thrived well until the day of admission when he developed convulsion, apnea and sudden cardiac arrest. Initially he was brought to a private hospital in Bangkok and subsequently referred to the Intensive Care Unit, Department of Pediatrics, Siriraj Hospital (March 29, 1998). During the first episode of cardiac arrest; hemoglobin was 10.9 g/dl, hematocrit 34 per cent, white blood cells 16,100/mm^3 with normal differential and platelets. Urine examination was normal except trace ketone. Blood chemistry values were normal except bicarbonate 14 mmol/L. Liver function tests were normal and plasma ammonia 415 Umol/L; cardiac enzymes : LDH 862, 2135, 1439 U/L, CPK 935, 2215 U/L and serum lactate 44 mmol/L. He was resuscitated successfully and discharged to a regular ward for observation for several days. Quantitative plasma amino acid analysis was within normal limits. He was discharged in good condition after 12 days and told to return to the Genetics clinic within 2 weeks. His dried blood spot was also sent for tandem mass spectrometry which was reported to be normal. The baby developed a second episode of sudden cardiac arrest (on April 19, 1998) and was admitted to another hospital in Bangkok where he expired after seven hours of attempted resuscitation failed. The result of urine organic acids by GC/MS which came after expiration, confirmed diagnosis of medium-chain acyl CoA dehydrogenase deficiency (Fig. 4).

Case Report 3 : Carnitine deficiency, systemic primary (CDSP). (OMIM 212140) (K.S.) A one-year-old girl presented with a history of progressive dyspnea since birth and parental consanguinity (Fig. 5). Initial diagnosis was endocardial fibroelastosis. Upon the second hospital admission, dilated cardiomyopathy was appreciated *via* echocardiogram. She developed a few episodes of cardiac decompensations and received aggressive supportive treatment. Physical examination revealed hepatomegaly, anemia and generalized hypotonia. There were no episodes of hypoglycemia. She later developed severe dyspnea and progressive congestive heart failure which got worse and subsequently progressed to cardiac arrest. Hemoglobin was 11.1 g/dl, hematocrit 31.3 per cent, white blood cells 9,580 mm^3 with normal differential and platelets. Urinaly-

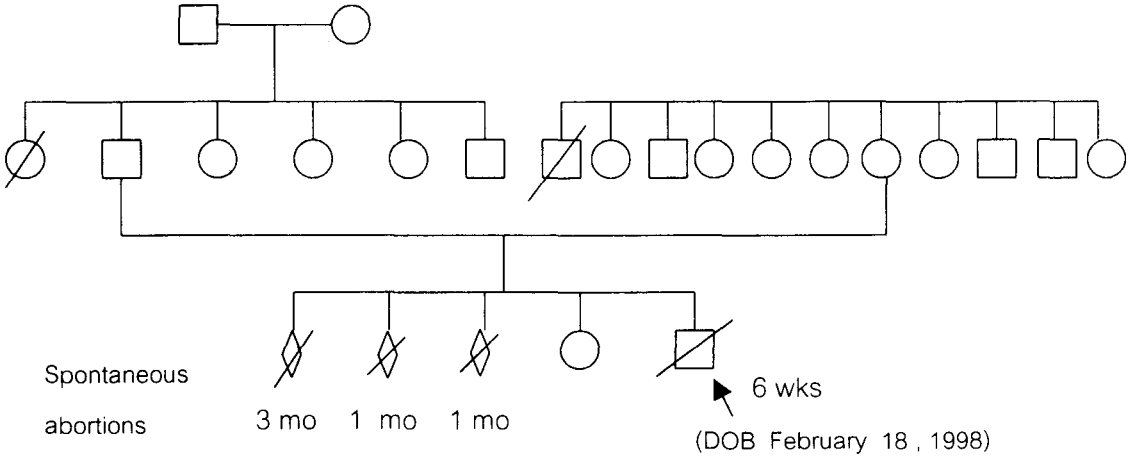

Fig. 3. Demonstrates family pedigree of patient with MCADD.

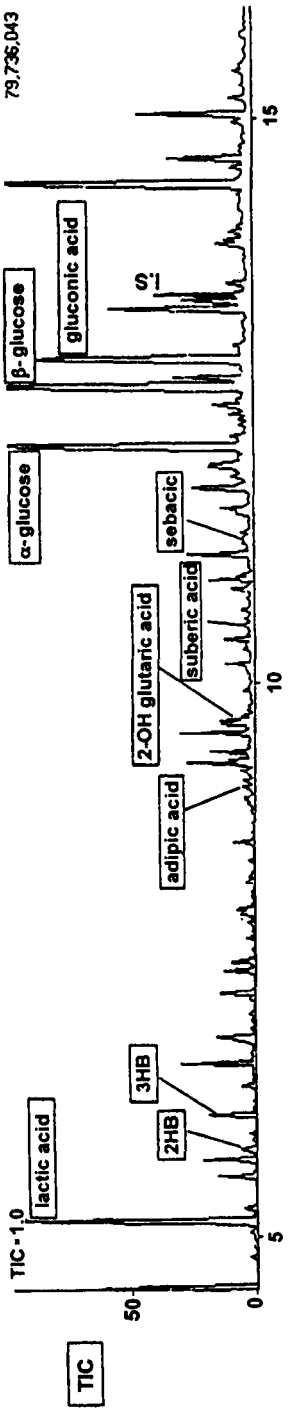

Fig. 4. Result of urinary compounds analysed by GC/MS : The increased excretion of lactic acid was found and increased amounts of 2-hydroxybutyric acid and 3-hydroxybutyric acid were also detected in the urine. In addition, the index compounds of medium chain acyl-CoA dehydrogenase deficiency (MCAD), adipic acid, malic acid, suberic acid and sebacic acid were detected in a large amounts together with the excess amounts of lactic acid.

sis was normal. Blood chemistry was within normal limits except bicarbonate 16 mmol/L. Chest radiograph showed CT ratio of 0.7 and echocardiogram demonstrated dilated cardiomyopathy and markedly left venticular dilatation with greatly reduced left ventricular ejection fraction 20 per cent (Fig. 6). Investigation prior to her death included normal urine organic acids analysis; however, the dried blood spot for tandem mass spectrometry demonstrated extremely low carnitine levels; free carnitine = <1 μM (normal 20-125); total acylcarnitine = 5 μM (normal 5-20); total carnitine = 5 μM (normal 25-125).

RESULTS

This report describes three infants with mitochondrial fatty acid oxidation disorders, all of which are the first such reported cases in Thai infants.

Patient 1. A 2-day-old male newborn, (DOB-August 22,1995) who developed sudden cardiac arrest at 48 hours of age with a previous history of early death (48 hours) in two other siblings with similar episodes of ventricular arrythmias and cardiorespiratory arrests, the defects were not documented. There was a history of parental consanguinity. The diagnosis of fatty acid oxidation disorder, most likely carnitine/acylcarnitine translocase deficiency, was made from dried blood spots using tandem mass spectrometry. The authors received the result after infant expiration and carnitine supplementation was not given prior to his death, due to unavailability of the product at the time. Since this is most likely the first reported case of fatty acid oxidation disorder in Thai infants, the authors were not able to treat him at that time.

Patient 2. A six-week-old male (DOB-February 18, 1998) infant who presented with cardiac arrest after a preceding viral illness, although he recovered after the first episode he subsequently succumbed to the second episode of sudden cardiac arrest. Analysis of the acylcarnitine profile *via* tandem mass spectrometry was normal; however, the urine organic acids analysis using gas-liquid chromatography and mass spectrometry confirmed the diagnosis of medium chain acyl CoA dehydrogenase deficiency in this patient. This is most likely the first reported case of MCAD in Thai infants. The patient was only 6 weeks old and MCAD deficiency was suspected on clinical grounds; however,

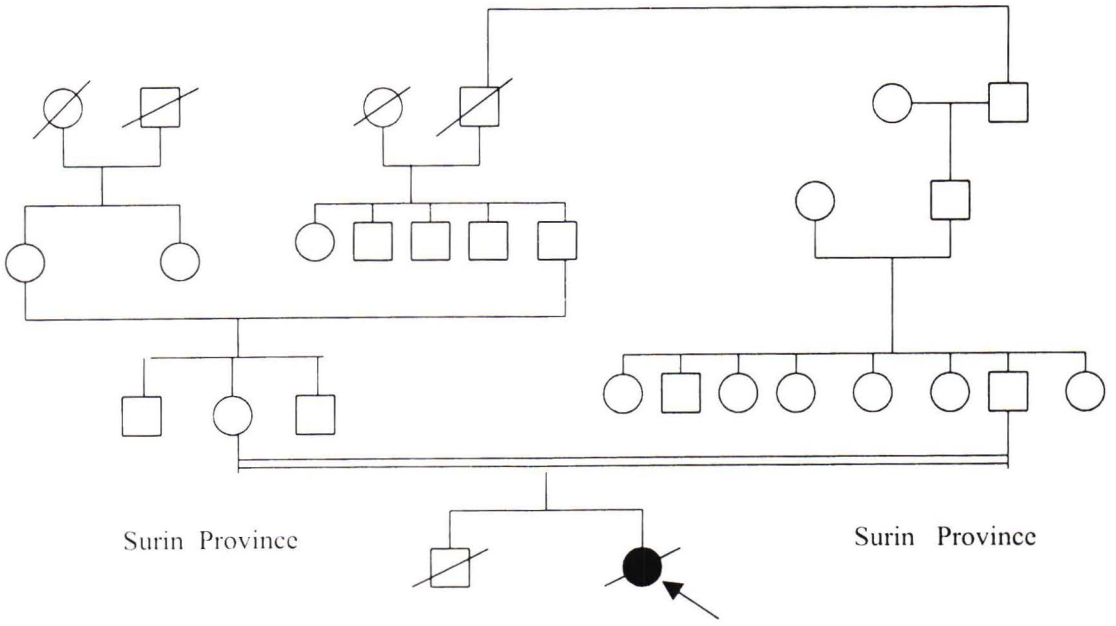

Fig. 5. **Parental consanguinity in a patient with carnitine deficiency, both from Surin province (Thai-Kmer extractions).**

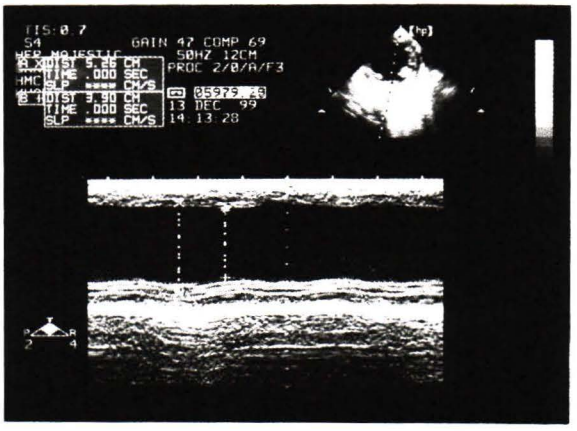

Fig. 6. **Demonstrates impaired left ventricular contractility with ejection fraction 20 per cent in a patient with carnitine deficiency.**

due to unfortunate circumstances and delayed confirmation, the authors were unable to confirm the diagnosis of MCAD prior to his second episode of cardiac arrest which caused death in this patient.

Patient 3. A one-year-old girl (DOB-December 13, 1998) with progressive cardiomyopathy, hepatomegaly and generalized hypotonia since birth; developed severe dyspnea, congestive heart failure and sudden cardiac arrest. Extremely low carnitine levels were found from dried blood spots *via* tandem mass spectrometry. This is apparently the first reported case of carnitine deficiency in a Thai infant presenting with dilated cardiomyopathy and congestive heart failure. Endocardial fibroelastosis was previously diagnosed in this patient, leading to delayed diagnosis and delayed treatment. Post-mortem examination of the liver demonstrated fatty infiltration. Since there was no well equipped metabolic center in Thailand at the time, the diagnosis was delayed. Death could have been prevented if carnitine supplementation had been given to this patient. This is most likely the first reported case of cardiomyopathy due to inborn errors of fatty acid oxidation in Thai infants.

DISCUSSION

Carnitine-acylcarnitine translocase deficiency (MIM 212138) is a rare and life-threatening

mitochondrial fatty acid beta-oxidation disorders[7]. It is an inherited defect of the cotransport of free and esterified carnitine across the inner mitochondrial membrane[6]. Stanley et al described the first patient with this defect in mitochondrial acylcarnitine transport in 1992[2,3]. A failure to transport long-chain acylcarnitines formed by CPT I leads to accumulation outside the mitochondrial matrix[5,6]. The neonatal phenotype of carnitine-acylcarnitine translocase (CACT) deficiency is one of the most severe and usually lethal mitochondrial fat oxidation disorders characterized by hypoketotic hypoglycemia, hyperammonemia, cardiac abnormalities, and early death[8]. When the deficiency is near total, it is usually fatal, affects life soon after birth, and constitutes one of the causes of skeletal muscle myopathy, cardiac and liver abnormalities, and childhood sudden death[7]. The presenting features include neonatal distress, convulsions, hypoglycemia, hyperammonemia, hypoketonuria, intermittent dicarboxyluria, hypothermia, apnea, neurological deterioration and hypocarnitinemia with grossly elevated acylcarnitines[4,5].

The diagnosis of fatty acid oxidation disorder, carnitine/acylcarnitine translocase deficiency in this patient, was made from dried blood spots (obtained during a resuscitation attempt which failed) using tandem mass spectrometry. Carnitine was not given to this patient due to unavailability of the product in Thailand at the time.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (MIM 212139) is the most common inborn error of fatty acid metabolism with significant mortality. It is an autosomal recessive disorder often present as a life-threatening disease in infancy[16]. Undiagnosed MCAD deficiency results in considerable mortality and morbidity[17]. It has been described in more than 200 patients worldwide, most of whom are of Northwestern European origin [9,10]. The most frequent manifestation is episodic hypoketotic hypoglycemia provoked by fasting and beginning in the first 2 years of life[11]. Sudden infant deaths syndrome (SIDS), recurrent Reye syndrome and episodic hypoglycemic coma have all been described in MCAD deficiency. The first episode can be devastating and result in sudden death[12-14]. Most patients present between 3-15 months of age[15].

The diagnosis of MCADD in patient 2 was made by urine organic acid analysis using gas-liquid chromatography mass spectrometry which demonstrated characteristic compounds; and most recently free fatty acid analysis using gas chromatography/mass spectrometry and dried blood spots[18,19]. Unfortunately, the results came too late, after his expiration.

Primary systemic carnitine deficiency (SCD) (OMIM 212140) is an autosomal recessive disorder of fatty acid oxidation caused by defective cellular carnitine transport. The disease is characterized by metabolic derangement simulating Reye's syndrome, hypoglycemia, progressive cardiomyopathy and skeletal myopathy. SCD has also been linked to sudden infant death syndrome[20]. Carnitine is required for entry of long-chain fatty acids into mitochondria where beta-oxidation occurs. The nutritional management of these disorders includes a high-carbohydrate, low-fat diet and avoidance of those events that promote fatty acid oxidation, such as fasting, prolonged exercise and cold. Large-dose carnitine treatment is effective in SCD[21,22]. Oral supplementation with L-carnitine has been reported to be useful in the treatment of both primary and secondary carnitine deficiency[23]. It has long been known that systemic carnitine deficiency is a treatable cause of cardiomyopathy[21,23].

Defects of the carnitine cycle or carnitine transport defect was first described in 1988. The ethnic distribution included Caucasian, African-American, North African Arab, Asian Indian, Mexican and Chinese[22,24]. Half of the reported patients presented early (3 months to 2.5 years) with episodes characterized by hypoketotic hypoglycemia, hyperammonemia and cardiomyopathy and/or skeletal muscle weakness. Cardiomyopathy alone was the presenting sign in half of the cases; usually of later onset (1-7 years)[21,22]. The diagnosis of carnitine deficiency in patient 3 was made from dried blood spots which was obtained during resuscitative efforts prior to her death using tandem mass spectrometry.

SUMMARY

Fatty acid oxidation disorders (FAO) can be detected by tandem mass spectrometry using Guthrie card as shown in patients with carnitine/acylcarnitine translocase deficiency and carnitine deficiency, systemic primary (CDSP). Urine organic acids analysis *via* gas-liquid chromatography and mass spectrometry can also detect FAO disorders e.g. medium chain acyl CoA dehydrogenase deficiency as reported in our patient. Recently, free fatty acid analysis using dried blood spots has also

confirmed diagnosis of FAO disorders. Undiagnosed, FAO disorders result in considerable mortality and morbidity. The introduction of tandem mass spectrometry to newborn screening has expanded the ability to diagnose metabolic diseases in the newborn period.

Mitochondrial fatty acid oxidation disorders, particularly MCAD deficiency, have been reported worldwide, mostly of Northwestern European ethnic background. In Asia, there have been reports from India and China but none from Japan. This report describes three infants with carnitine/acylcarnitine translocase deficiency; medium-chain acyl CoA dehydrogenase deficiency (MCADD) and carnitine deficiency systemic primary (CDSP), all of whom are the first such cases in Thai infants.

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โรคที่มีความบกพร่องในการสังเคราะห์กรดไขมันในไมโตคอนเดรีย : รายงานในผู้ป่วยไทย 3 ราย†

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รายงานนี้เกี่ยวกับผู้ป่วยเด็กไทย 3 รายที่เป็นโรคพันธุกรรมเมตาบอลิคที่มีความบกพร่องในการสังเคราะห์กรดไขมันในไมโตคอนเดรีย รายที่ 1 Carnitine/acylcarnitine translocase deficiency. (CACT) – เด็กชายอายุ 2 วัน มีหัวใจหยุดเต้นฉับพลันในวันที่ 2 หลังคลอด โดยมีประวัติพี่น้องท้องเดียวกันเสียชีวิตด้วยอาการเหมือนกันในวันที่ 2 อีก 2 คน และมีประวัติพ่อแม่เป็นญาติกัน ผู้ป่วยมีอาการปลุกไม่ตื่น ไม่ดูดนม ตับโต มีภาวะน้ำตาลในเลือดต่ำ ภาวะแคลเซียมในเลือดต่ำ ภาวะโปตัสเซียมในเลือดต่ำ และภาวะกรดคั่งมากในเลือด ก่อนที่มีอาการหัวใจหยุดเต้น การเจาะเลือดใส่กระดาษกรองและส่งตรวจโดยวิธี tandem mass spectrometry พบมีระดับ palmitoyl carnitine สูงเป็น 10 เท่าของปกติ oleylcarnitine, steroylcarnitine และ myristoylcarnitine สูงระดับปานกลางในเลือด รายที่ 2 Medium chain acyl CoA dehydrogenase (MCAD) deficiency. – เด็กชายอายุ 6 สัปดาห์ มีอาการหัวใจหยุดเต้นฉับพลันภายหลังได้รับเชื้อไวรัส ได้รับการช่วยเหลือฟื้นคืนชีพในครั้งแรก แต่เสียชีวิตในอีก 2 สัปดาห์ต่อมา ระดับ acylcarnitine ในเลือดโดยการตรวจด้วย tandem mass spectrometry รายงานผลปกติ แต่การตรวจปัสสาวะโดยวิธี gas liquid chromatography และ mass spectrometry พบสารเมตาบอไลท์ที่มีลักษณะจำเพาะของ MCADD รายที่ 3 Carnitine deficiency, systemic primary. (CDSP). – เด็กหญิงอายุ 1 ปี มีอาการหายใจหอบเหนื่อยตั้งแต่แรกเกิด มีประวัติการแต่งงานในเครือญาติ พบหัวใจโตมากแบบ dilated cardiomyopathy และมีภาวะหัวใจล้มเหลว ตับโต ซีดและกล้ามเนื้ออ่อนปวกเปียก แต่ไม่มีภาวะน้ำตาลในเลือดต่ำก่อนหัวใจหยุดเต้น พบระดับ carnitine ในเลือดต่ำมากในกระดาษกรองซับเลือดและส่งตรวจโดยวิธี tandem mass spectrometry

คำสำคัญ : โรคที่มีความบกพร่องในการสังเคราะห์กรดไขมันในไมโตคอนเดรีย, mitochondrial disorders, sudden cardiac arrest, ภาวะหัวใจหยุดเต้นฉับพลัน, cardiomyopathy

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