Maple Syrup Urine Disease in Thai Infants

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Maple syrup urine disease (MSUD) is a rare inborn error of metabolism, caused by a deficiency in activity of the branched chain alpha-keto acid dehydrogenase impairing the degradation of the branched-chain amino acids (leucine, isoleucine and valine). Classic MSUD usually manifests in the neonatal period with poor feeding, vomiting, lethargy, muscular hypertonicity, seizure, coma and death. Thirteen cases of classic MSUD were diagnosed from 1997-2007 at the Queen Sirikit National Institute of Child Health. All cases presented in the neonatal period. The onset of symptoms ranged from 3 to 20 days (median 8 days). The time taken to make the diagnosis ranged from 18 to 356 days (median 55 days). The diagnosis was accomplished by clinical diagnosis and confirmed by detecting abnormal levels of amino acids in the blood and organic acids in the urine. Clinical manifestations were non-specific such as poor suck, weak cry, drowsiness and seizures. Majority of cases were initially diagnosed as sepsis and/or meningitis. All patients had neurological sequelae and psychomotor retardation. This results show the need for increase awareness of metabolic disorder such as MSUD and the requirement for early detection and treatment to ensure a better outcome.

Keywords: *Maple syrup urine disease, Branched-chain amino acids*

J Med Assoc Thai 2008; 91 (Suppl 3): S41-4
Full text. e-Journal: *http://www.medassocthai.org/journal*

Maple syrup urine disease (MSUD) is caused by deficiency of the branched-chain alpha-keto acid dehydrogenase enzyme complex characterized by elevated plasma levels of branched-chain amino acids and urinary excretion of branched-chain keto acids[1-4]. MSUD is inherited in an autosomal recessive mode, with an incidence of 1 in 185,000[5]. It is more prevalent in populations with a high frequency of consanguinity. The disease was first described in 1954 by Menkes, Hurst and Craig who observed an unusual odor like that of maple syrup in the urine of four infants who died of a progressive neurological disease in the first weeks of life[6]. Several forms of this condition have been reported, classic MSUD is the most common form and the most severe clinical manifestation[5]. Infants with MSUD appear normal at birth. Usually by the end of the first week, they become lethargic and develop progressive neurological deterioration. If the disease is untreated, they proceed to seizure, cerebral edema, apnea, coma and death usually occurring within the first month of life[7,8]. Treatment with a low protein diet supplemented with a branched-chain-free amino acids mixture is successful[9-14]. In the present study, the authors describe thirteen cases of classic MSUD in Thai infants with clinical presentation, laboratory profiles, treatment and outcome of all patients.

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Material and Method

Medical records of patients with the diagnosis of MSUD admitted at the Queen Sirikit National Institute of Child Health from 1997 to 2007 were reviewed. All patients were diagnosed to have MSUD by

clinical features and confirmed by analysis of amino acids from dried blood spot samples using tandem mass spectrometry, plasma amino acid analysis using high performance liquid chromatography (HPLC) and urine organic acid analysis using gas chromatography and mass spectrometry (GC/MS). Laboratory data as well as information on clinical course and management were analyzed. Descriptive statistics were used for data analysis.

Results

A clinical profile of the thirteen cases with MSUD is shown in Table 1. There were seven males and six females. All cases were born at term after an uneventful pregnancy except one of them was preterm newborn infant. The median birth weight was 3.1 kg. All were in good condition at birth except for one who was preterm with respiratory distress. The onset of symptoms ranged from 3 to 20 days, median age was 8 days. The onset of diagnosis ranged from 18 to 356 days, median age was 55 days. All of the cases were referred from other hospitals to the Queen Sirikit National Institute of Child Health. Consanguinity marriage was found in four cases (30.7%). Sibling death with similar symptoms was found in seven cases (53.8%).

The presenting signs and symptoms of the patients are shown in Table 2. All patients had poor feeding and lethargy after feeding. Other common features included seizures (5 of 13), persistent metabolic acidosis (10 of 13), sweet smelling urine odor (5 of 13) and hypoglycemia (2 of 13). Ten patients were diagnosed before admission with sepsis and/or meningitis. They were initially treated with antibiotics without improvement. Another two cases had diagnosed with spastic cerebral palsy.

The results of diagnostic procedures of all patients are shown in Table 1. Four cases were confirmed diagnosis with plasma amino acid analysis, one case with urine organic acid analysis, three cases with plasma amino acid analysis and urine organic acid analysis, four cases with tandem mass spectrometry and urine organic acid analysis, one case using tandem mass spectrometry, plasma amino acid analysis and urine organic acid analysis. The results of amino acid and organic acid analysis showed marked elevation of

Table 1. Clinical profile of 13 cases with MSUD

Case No.	Sex	Birth weight (kg)	Age of onset (day)	Age at diagnosis (day)	Consanguinity	Sibling dead with similar symptoms	Confirmatory methods
1	M	2.7	9	40	-	-	Plasma amino acid analysis
2	M	3.1	8	90	-	-	Plasma amino acid analysis, Urine organic acid analysis
3	F	3.5	5	85	+	+	Plasma amino acid analysis
4	F	3.9	5	73	+	+	Plasma amino acid analysis
5	F	3.5	8	27	-	+	Plasma amino acid analysis, Urine organic acid analysis
6	F	3.1	12	43	-	-	Urine organic acid analysis
7	M	3.5	3	43	-	-	Plasma amino acid analysis
8	M	2.7	10	356	-	+	Tandem mass spectrometry, Urine organic acid analysis
9	M	1.6	3	22	+	+	Tandem mass spectrometry, Plasma amino acid analysis, Urine organic acid analysis
10	F	2.5	8	55	-	-	Tandem mass spectrometry, Urine organic acid analysis
11	M	3	20	175	-	+	Tandem mass spectrometry, Urine organic acid analysis
12	F	3.8	5	18	+	+	Tandem mass spectrometry, Urine organic acid analysis
13	M	3.9	10	112	-	-	Plasma amino acid analysis, Urine organic acid analysis

Table 2. Presenting signs and symptoms of 13 cases with MSUD

Signs and symptoms	No.	%
Poor feeding	13	100
Drowsiness, lethargy	13	100
Seizures	5	38.5
Sweet smelling urine odor	5	38.5
Persistent metabolic acidosis	10	76.9
Hypoglycemia	2	15.4

branched-chain amino acids and their metabolites consistent with MSUD.

Discussion

From the present study, thirteen cases of MSUD were diagnosed on clinical grounds. All cases appeared normal at birth. Signs and symptoms of disease did not appear for several days and weeks. Vomiting and poor feeding were found as early symptoms and they became lethargic and progressive neurological deterioration rapidly. Age of onset of illness ranged from 3 to 20 days (median 8 days) but the age when diagnosis was made ranged from 18 to 356 days (median 55 days). All of the patients were diagnosed to have MSUD rather late, except for patient No.12, who had a history of a previously-affected sibling with MSUD, and was diagnosed at age 18 days. This delay was caused by many factors including screening for MSUD's not being an integral part of the newborn screening in Thailand, lack of awareness concerning inborn error in metabolism, and difficulty in diagnosis due to lack of available laboratory testing in up-country hospitals. All of our patients started treatment immediately after diagnosis with enteral or parenteral nutritional treatment using branched-chain-free amino acid mixture, low protein diet, adequate hydration and caloric intake. After initial management and dietary therapy, clinical improvement was observed. However, one patient (No. 9) died after admitted to the hospital for 4 months due to chronic lung disease and sepsis and another patient (No. 13) developed acrodermatitis enteropathica-like skin rash due to amino acid deficiency. Psychomotor development was delayed in all patients except case No. 12, who was diagnosed relatively early. Dietary treatment was suggested to be continued throughout the patient's life because these patients suffering from MSUD are unable to metabolize branched-chain amino acids which are present in all protein foods.

MSUD is inherited as an autosomal recessive trait; the recurrent risk for a further child is 1 in 4. From the present study, consanguinity marriages were found in four families; sibling deaths with similar symptoms were suspected to have had the same condition and were also found in seven families. Therefore genetic counseling is very important and should be provided to all families. Prenatal diagnosis is also currently available. The neonatal screening is beneficial for patients in early detection and treatment.

In conclusion, the MSUD infants, who are not detected, are easily missed especially in early infant death because of a diagnosis of sepsis; once it is known that a family has this condition, the other siblings in the family should be watched with great care. From the present study, the time taken to make the diagnosis after the first symptoms is the important factor determining the outcome. It emphasizes that early diagnosis and prompt corrective treatment are very important for MSUD to prevent mental retardation and death.

Acknowledgements

The authors would like to thank to the Department of Medical Sciences, Ministry of Public Health, the Queen Sirikit National lnstitute of Child Health, the Chulabhorn Research Institute for their help and laboratory supports. We would like to thank the Mead Johnson Nutritional Products (Thailand) for providing special diet for these patients.

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โรคปัสสาวะกลิ่นเมเปิลไซรับในทารกไทย

สุทธิพงษ์ ปังคานนท์, วิยะดา เจริญศิริวัฒน์, วราภรณ์ แสงทวีสิน

โรคปัสสาวะกลิ่นเมเปิลไซรับ เป็นโรคพันธุกรรมเมตาบอลิกชนิดหนึ่งที่พบได้น้อย สาเหตุเกิดจากการขาดเอนไซม์ branched chain alpha-keto acid dehydrogenase ทำให้ไม่สามารถย่อยสลายกรดอะมิโนแบบมีก้านได้ ผู้ป่วยโรคนี้มักมีอาการตั้งแต่ในช่วงทารกแรกเกิด อาการทางคลินิกได้แก่ ดูดนมได้น้อย อาเจียน ซึม กล้ามเนื้อเกร็ง ชัก ไม่รู้สึกตัวและเสียชีวิต ผู้นิพนธ์ได้รายงานผู้ป่วยโรคปัสสาวะกลิ่นเมเปิลไซรับจำนวน 13 ราย ซึ่งทั้งหมดได้รับการตรวจวินิจฉัยที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ตั้งแต่ปี พ.ศ. 2540 ถึง พ.ศ. 2550 ผู้ป่วยทุกรายมีอาการตั้งแต่ในช่วงทารกแรกเกิด โดยอาการแสดงเริ่มต้นมีช่วงอายุตั้งแต่ 3 ถึง 20 วัน (ค่ากลาง 8 วัน) ระยะเวลาที่ได้รับการวินิจฉัยโรคมีช่วงอายุตั้งแต่ 18 ถึง 356 วัน (ค่ากลาง 55 วัน) ผู้ป่วยทุกรายได้รับการวินิจฉัยจากอาการทางคลินิกร่วมกับการตรวจยืนยันทางห้องปฏิบัติการ โดยตรวจพบว่ามีความผิดปกติของระดับกรดอะมิโนในเลือดและกรดอินทรีย์ในปัสสาวะ ผู้ป่วยมีอาการแสดงทางคลินิกที่ไม่เฉพาะเจาะจงได้แก่ ดูดนมได้น้อย ร้องเสียงเบา ซึม และชัก ผู้ป่วยส่วนใหญ่ได้รับการวินิจฉัยเบื้องต้นว่ามีภาวะติดเชื้อในกระแสโลหิตร่วมกับภาวะเยื่อหุ้มสมองอักเสบ ภายหลังการรักษาผู้ป่วยทุกรายยังคงมีความผิดปกติทางระบบประสาทหลงเหลืออยู่ จากผลการศึกษาดังกล่าวบ่งชี้ว่าการตรวจวินิจฉัยและให้การรักษาที่รวดเร็วจะช่วยให้ผลการรักษาที่ออกมาดี