Urea Cycle Disorders in Thai Infants : A Report of 5 Cases†

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Abstract

Urea Cycle Disorders (UCD) is an inborn error of urea synthesis in which ammonium and other nitrogenous precursors of urea accumulate leading to episodic coma and a high mortality rate. Therapy with peritoneal dialysis, essential amino acids or their nitrogen-free analogues has increased survival. The authors report 5 cases of urea cycle disorders, all of whom developed and were rescued from hyperammonemic coma. However, the eventual outcome was quite variable.

Argininosuccinate lyase deficiency (ALD) Case 1. A 2 month old male infant, a product of a consanguineous marriage (Suphanburi province); developed poor feeding on day 7, lethargy, convulsion, hepatomegaly and respiratory alkalosis leading to respiratory failure and coma. Hyperammonemia, elevation of glutamic acid and argininosuccinic acid and its anhydrides confirmed the diagnosis of ALD. He is now 9 years old and severely retarded. **Case 2.** A male infant with history of lethargy, poor feeding on day 3, treated as sepsis and required respiratory support for 6 days; subsequently readmitted at age 2 weeks with vomitting, lethargy, seizure activity and hyperammonemia, and was treated by a local pediatrician in Songkhla province. There was a history of parental consanguinity and he was referred to Siriraj Hospital on day 64 with severe essential amino acid deficiency and acrodermatitis enteropathica with markedly elevated plasma citrulline level. In spite of aggressive treatment; the patient developed sepsis and he expired on day 78.

Ornithine transcarbamylase deficiency (OTC) Case 3. An eleven-month-old male infant, the product of a non-consanguineous marriage, developed neonatal onset of hyperammonemia on day 5 after poor feeding, lethargy, hypothermia, seizure, apnea and coma. He was rescued from neonatal hyperammonemic coma on day 9 after aggressive treatment, but expired at eleven months of age after overwhelming sepsis. **Case 4.** A male infant, sibling of case 3 was referred to Siriraj Hospital on day 8 with hyperammonemia and coma. In spite of intensive genetic counseling given after the birth of their first child with OTC, the couple chose to have another baby without informing any physician. The baby developed vomiting and lethargy on day 2; subsequently hyperammonemia was noted. In spite of aggressive treatment given; hepatic dysfunction, renal failure and disseminated intravascular coagulation defects occurred on day 15. He expired on day 18 after parental permission for discontinuation of all treatment.

Argininosuccinate synthetase deficiency (ASS) or Citrullinemia. Case 5. A seven week old female infant, the product of a consanguineous marriage and of Pakistani ethnic origin; developed intermittent vomiting from day 6. Initial diagnoses included ruminations, sepsis and pyloric stenosis for which she was operated on (day 30); however, vomiting continued; subsequently seizures, hyperammonemic coma developed and she was rescued from hyperammonemic coma within 30 hours. Significant elevations of citrulline and L-glutamine were demonstrated. She was discharged in excellent condition to her home in Dubai, the United Arab Emirates.

Key word : Urea Cycle Disorders, Hyperammonemia, ALD, OTC, ASS, Metabolic Encephalopathy

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The urea cycle serves two purposes: 1). it contains the biochemical reactions required for the de novo biosynthesis and degradation of arginine, and 2). it incorporates nitrogen atoms not retained for net biosynthetic purposes into urea, which serves as a waste nitrogen product (Brusilow SW, Horwich AL. Urea Cycle Enzymes. In : The Metabolic and Molecular Bases of Inherited Disease, 8th edition, New York, McGraw-Hill, 2001, 1909-1963). Five well-documented diseases have been described, each representing a defect in the biosynthesis of one of the enzymes of the urea cycle. Four of these five diseases, deficiencies of carbamyl phosphate synthetase (CPSD), ornithine transcarbamylase (OTCD), argininosuccinic acid synthetase (ASD), and argininosuccinase (ALD), are characterized by signs and symptoms induced by the accumulation of precursors of urea, principally ammonium and glutamine[1-3]. The most dramatic clinical presentation of these four diseases occurs in full-term infants with no obstetric risk factors and who appear normal for the first 24-48 hours and then exhibit progressive lethargy, hypothermia and apnea all related to very high plasma ammonium levels. The encephalopathy is characterized by brain edema and swollen astrocytes, due to intraglial accumulation of glutamine resulting in osmotic shifts of water into the cell. All five diseases, with the exception of ornithine transcarbamylase deficiency which is inherited as an X-linked recessive disorder, are inherited as autosomal recessive disorders[4,5].

Treatment requires restriction of dietary protein intake and activation of other pathways of waste nitrogen synthesis and excretion. For patients deficient in carbamyl phosphate synthetase, ornithine transcarbamylase and argininosuccinic acid synthetase, treatment with sodium phenylbutyrate activates the synthesis of phenylacetylglutamine, which serves as a waste nitrogen product[3]. In patients with argininosuccinic acid synthetase and argininosuccinase, supplementation of the diet with arginine promotes the synthesis of citrulline in the former and argininosuccinate in the latter, both of which serve as waste nitrogen products[6,7].

Clinical presentation with CPS, OTC, AS and AL deficiencies are virtually identical, but with great variability. They may appear in the neonatal period and be fatal or they may appear later with varying degrees of severity. Hyperammonemia is common and may lead to encephalopathy[7]. The clinical course of the neonatal - onset group is very typical; an infant, almost always the product of a full-term normal pregnancy with no known prenatal and perinatal risk factors and normal labor and

delivery and appears normal in the first 24 hours. Later the infant becomes lethargic and develops poor feeding or vomiting, hypothermia and hyperventilation. A work up for sepsis usually reveals normal results. Serum urea nitrogen may be as low as 1 mg/dl. Without intervention, the infant becomes comatose, requiring mechanical ventilation. CT scan usually reveals cerebral edema. The family history is often neglected. Parental consanguinity, neonatal sib deaths or neonatal male deaths is frequent. The major symptoms of the later - onset group include vomiting, abnormal mental status manifested by lethargy, somnolence often progressing to coma, irritability, agitation, disorientation, ataxia and amblyopia. Seizures, delayed physical growth and developmental delay are common[8,9].

MATERIAL AND METHOD

Case Report

Case 1. (J.C.) A two-month- old boy was born at a private hospital in Bangkok (DOB May-24-1993), birth weight 3,430 g, height 50 cm, and head circumference 35 cm. Apgar scores 9, 10 respectively. He developed hyperbilirubinemia on day 2 and was breast fed. He started to feed poorly on day 7, vomitted and became stuporous with 430 g weight loss and required hospitalization. He developed hypotonia and laboratory data showed : CBC-Hct 51 per cent, WBC 16,400/mm^3, (N 35%, L 64%, E 1%), platelet 204,000/mm^3; serum electrolytes (Na 157, K 5.1, Cl 125, HCO3 16 mmol/l); BUN 4 mg/dl, Cr 0.4 mg/dl; LFT - total protein 7 g/dl, alb/glob 4.2/2.8 g/dl, direct bili/total bili 3.6/6.0 mg/dl, AST/ALT 99/59 U/L, alkaline phosphatase 290 U/L, bilirubin 25 mg per cent. Sepsis work up was done including lumbar puncture which was normal. Exchange transfusion was done and followed by phototherapy. He developed focal seizure and irregular respiration requiring ventilatory support. Hepatomegaly was noted (4 cm below RCM). He was also found to have G6PD deficiency. He was hospitalized for 21 days and discharged on a regular formula and the mother reported that the baby fed well.

He was readmitted at age 6 weeks with somnolence, vomiting, continuous whining and massive hepatomegaly (liver 7 cm below RCM). Hepatic encephalopathy developed when plasma ammonia was 310 Umol/L; subsequently he had exchange transfusions and was placed on respiratory support. LFT (July 1993) - total protein 5.0 g/dl, alb/glob 3.1/1.9 g/dl, DB/TB 0.1/0.2 mg/dl, AST/ALT

Pedigree :

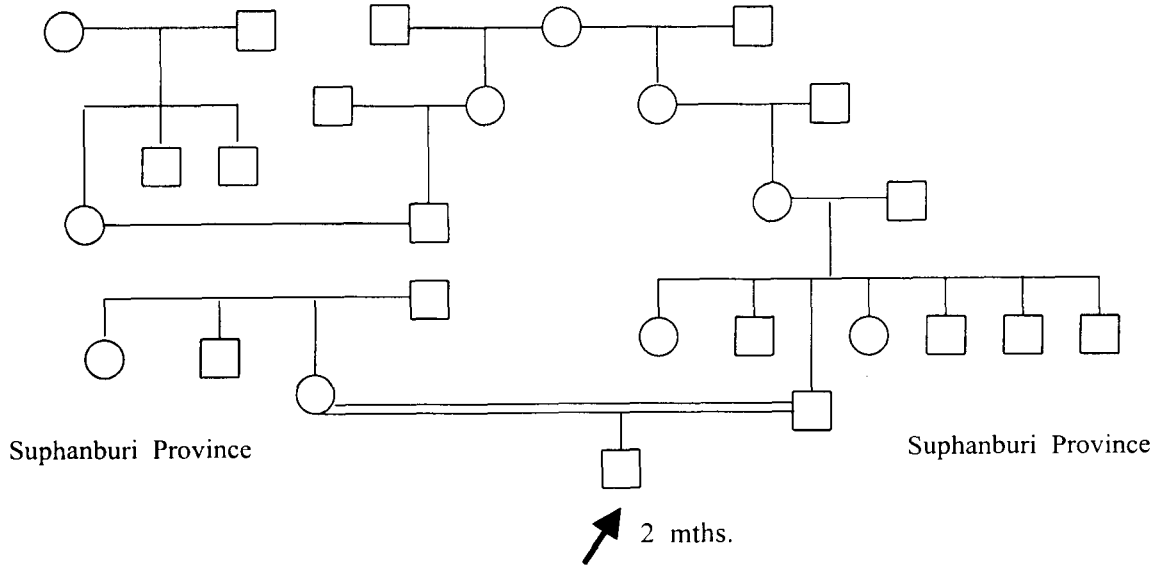

Fig. 1. A pedigree demonstrated parental consanguinity (case 1).

45/86 U/L, alkaline phosphatase 314 U/L, Ca 8.1 mg/dl, phosphorous 3.8 mg/dl. A clinical geneticist was consulted at this stage when inborn error of metabolism was considered. It was discovered that the parents were related. He was subsequently referred to Siriraj Hospital for further work up and treatment. Upon admission, hyperammonemia and massive hepatomegaly (liver 7 cm below RCM), increased tone upon crying were noted. He was placed on Prosobee (120 ml x 6), later changed to Olac due to lower protein content, since the authors did not have low protein formula at the time. Plasma amino acid analysis was sent to the Genetics Laboratory, Kennedy Institute in affiliation with the Johns Hopkins Hospital, Baltimore, Maryland, USA which identified the argininosuccinic acid and its anhydrides, confirmed the diagnosis of argininosuccinic acid lyase deficiency (ALD). He was placed on protein 1.5 g/kg/day of regular formula (Olac, Prosobee) until the UCD I formula (Ross Laboratories, USA) could be obtained.

His developmental assessment at age 9 months demonstrated that he was alert to sound, soothed when picked up with social smiling, cooing and orientation to voice. His CLAMS DQ = 39, CAT DQ = 37; CAT-CLAMS-DQ = 38 (severe mental retardation). However later neurological evaluation revealed inconsolable crying, opisthotonic posturing, severe microcephaly, no head control, hyperreflexia. Severe psychomotor delay with spastic quadriplegia was noted. Genetic counseling was given throughout, 25 per cent risk of recurrence was emphasized and contraception was advised. Limitation of availability of appropriate special formula (UCD) and inability to perform prenatal diagnosis in Thailand were conveyed to the parents including importance of regular follow-up. However, both parents decided to have another pregnancy within a year. A girl was born in April 1994, now two years old and is developmentally normal.

Case 2. (W.S.) A 3-month-old boy was referred to Siriraj Hospital suspected to have urea cycle disorder on May 7, 2001. He was born at a local hospital in Hat Yai, southern Songkhla province, a term product of consanguineous parents, birth weight 3,340 g after normal pregnancy and delivery (DOB February 3, 2001). He did well until day 3 when he became lethargic, refused feedings and was admitted for sepsis. He had apnea and required respiratory support for 6 days. At age 2 weeks, he vomitted and again became lethargic, had increased muscle tone and was readmitted when hyperammonemia was noted (plasma NH_3 703 Umol/L). The diagnosis of urea cycle was made and he

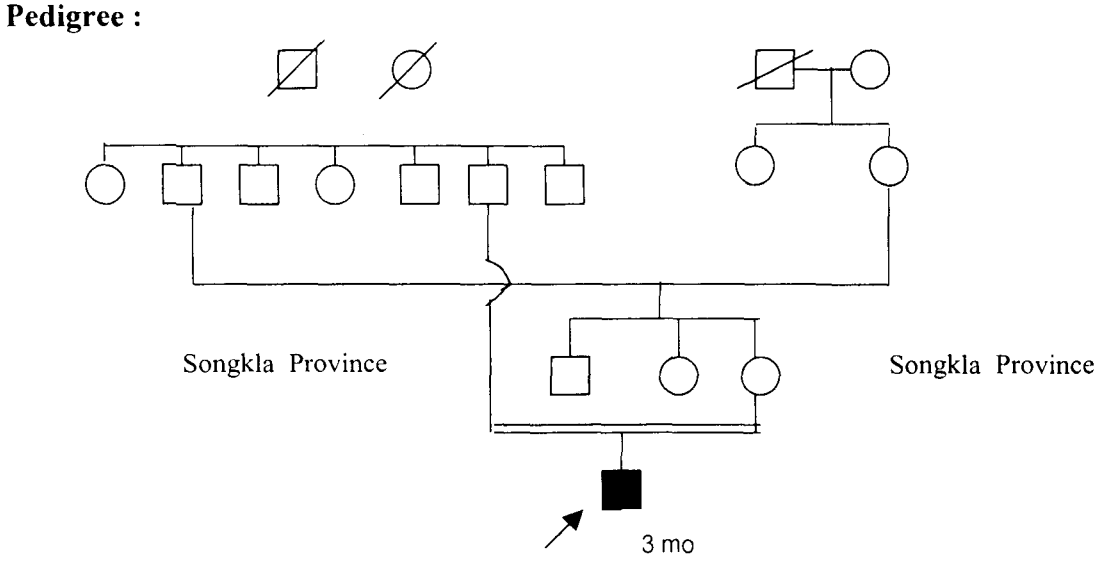

Fig. 2. A pedigree demonstrated parental consanguinity (case 2).

was placed on a non-protein diet (Dextrin). Subsequently acrodermatitis enteropathica developed with persistent metabolic acidosis.

He was referred to Siriraj Hospital on day 90 when severe essential amino acid deficiency developed with sepsis. Laboratory data showed : CBC - Hct 30 per cent, Hb 10 g/dl, WBC 14,200/mm^3, (N35%, L 46%, Mono 14%, E 0.1%), platelet 539,000/mm^3; blood chemistry - sugar 138 mg/dl, BUN 1 mg/dl, Cr 0.2 mg/dl, serum electrolytes (Na 139, K 5.2, Cl 111, HCO_3^- 13 mmol/l), with anion gap 15, albumin 2.2 g/dl, globulin 1.7 g/dl; plasma ammonia 404, 104, 178, 801, 122 and 274 Umol/L respectively; urinalysis - sp gr 1.025, pH 6.0, protein 1+, sugar 3+, ketone - negative; urine metabolic screen-negative. Quantitative plasma amino acid demonstrated citrulline 888.65 nmol/ml, arginine 0. Serum lactate 10.6 mmol/L. Zinc level 50 μg/dl (normal 64-118 μg/dl). He received Product 80056 (Mead Johnson) and PPN with 0.5 g/kg/day of protein with broad spectrum antibiotics for sepsis, sodium benzoate 250 mg/kg, arginine 125 mg/kg/day → 700 mg/kg/day. However, in spite of aggressive treatment; he developed fungemia, renal insufficiency and expired on day 103.

Case 3. (N.C.) A four-month-old boy (DOB February-14-1996) was born at term, birth weight 2,990 g, after an uncomplicated pregnancy, labor and delivery. He was born at a private hospital in Bangkok and was fine until day 5 when he developed poor feeding, lethargy, hypothermia, hypertension, seizure, apnea and went into a coma. He was intubated and placed on a respirator and septic work up was done. Liver function was normal; glycosuria, proteinuria and ketonuria were observed. Plasma ammonia was 1,486 Umol/L (day 7) and 800 Umol/L (day 8). Total blood exchange done (x2) after which the baby had spontaneous respiration, spontaneous movement and subsequently transferred to Siriraj Hospital. On examination he was semicomatose with spontaneous respiration; hepatomegaly and generalized hypotonia were observed. Clinical diagnosis of urea cycle disorder, specifically OTC was suspected on clinical grounds.

Laboratory data showed : CBC - Hct 53 per cent, Hb 16 g/dl, WBC 5,400/mm^3, platelets 255,000/mm^3; urinalysis - pH 8, 7.5, protein 1+, ketone-negative; blood chemistry - sugar 68 mg/dl, BUN 2 mg/dl, Cr 0.4 mg/dl, serum electrolytes - (Na 132, K 2.4, Cl 100, HCO_3^- 25 mmol/l), calcium 4.5 mg/dl, phosphorus 7.3 mg/dl, magnesium 1.5 mg/dl. Plasma ammonia ranged from 1,486, 800, 1,001, 835 Umol/L initially and gradually decreased to 230, 355, 272 and 174 Umol/L, within 2 weeks. Quantitative amino acid analysis : urea 1,515, 1,963, 2,699 nmol/ml; glutamine 7,231, 361, 2,540 Umol/L; alanine 1,422, 566, 475 Umol/L; ornithine 0, 0, 864 Umol/L; arginine 36, 15, 0 Umol/L. The authors were not able to perform orotic acid. Management included exchange transfusion (x2) prior to referral and (x3) after admission to Siriraj Hospital, pediatric intensive care unit. Inability to perform peritoneal dialysis/hemodialysis

Pedigree :

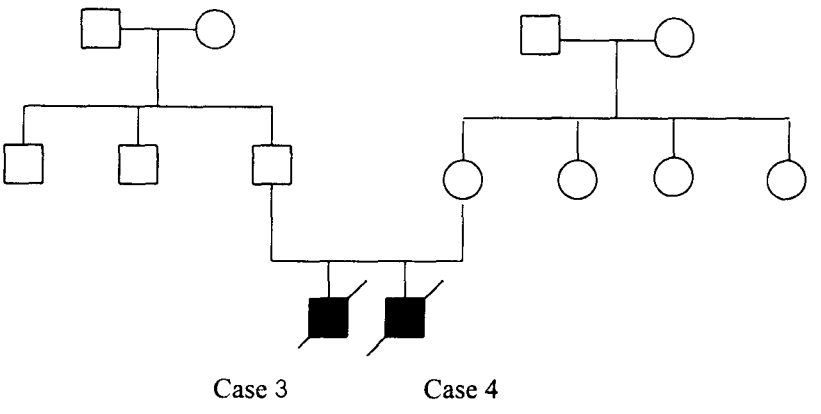

Fig. 3. A pedigree demonstrated 2 male siblings affected with OTC (case 3, 4).

made it very difficult to lower ammonia and glutamine levels. Administration of sodium benzoate and sodium phenylacetate to expedite renal excretion; L-arginine, ketosteril, intravenous fluids (TPN) with. 0.25 → 0.5 → 1 → 1.5 g/kg/d of protein as tolerated; Product 80056 alternating with regular formula given to provide caloric intake of 60 → 80 → 100 → 120 → 150 cal/kg/d (including intralipid). Plans to give sodium phenylbutyrate were discussed with the parents; however they declined. Subsequently be was readmitted several times with sepsis, pneumonia, URI and developed hyperammonemia (plasma ammonia 1,500 Umol/L) which was very difficult to control. He expired at age 11 months (January 1997); only 2 months after his death, his mother became pregnant again.

Case 4. (P.C.) A full term 2,660 g male infant (DOB November 13, 1997) was born at a private hospital in Bangkok, a younger sibling of case 3. He started to have some vomiting on day 2; however, plasma ammonia was not done until day 5 when the parents revealed the history of OTC in the older sib. He was then referred to Siriraj Hospital on day 8 with lethargy, poor feedings and hyperammonemia (plasma NH_3 365 Umol/L). Laboratory data on admission : CBC – Hct 58.8 per cent Hb 19.3 g/dl, WBC 13,730/mm^3, (N50%, L42%, M9%, E3%), platelets 501,000/mm^3; urinalysis - sp gr 1.021, pH 8, protein 1+, ketone - negative; BS 97 mg/dl, BUN 6 mg/dl, Cr 0.5 mg/dl; blood chemistry- Na 151, Cl 119, K 5.7, HCO_3^- 16 mmol/l; serum calcium 3.6 mg/dl, magnesium 2.1 mg/dl; plasma ammonia 559 Umol/L. Sepsis work up was negative for organisms. Quantitative plasma amino acid demonstrated elevation of glutamine. Treatment consisted of intravenous fluids, sodium benzoate (250 mg/kg/day), sodium phenylbutyrate (500 mg/kg/day), arginine (400 mg/kg/day) with caloric intake (PPN) of 100-120 cal/kg/day and exchange transfusions (x2). However, plasma ammonia rose to 1,115 Umol/L on day 14 and disseminated intravascular coagulation defect developed. Parental permission to discontinue all treatment was finally given on day 28 when he expired.

Case 5. (N.P.) A seven-week-old baby girl (DOB September 25, 1999) born a term infant at a private hospital in Bangkok with a history of parental consanguinity (a Pakistani couple), developed vomiting intermittently from day 6. She was in and out of private hospitals in her first months of life and was diagnosed with pyloric stenosis for which she was operated on. However, the vomiting continued and plasma ammonia was obtained which was 668 Umol/L on day 53, after which she was transferred to Siriraj Hospital in a coma. Laboratory data : CBC - Hct 27 per cent, Hb 9 g/dl, WBC 13,000/mm^3, (N51%, L36.6%, M6.6%, E0.5%), plalelets 630,000/mm^3; urinalysis-sp gr 1020, pH 7.0, protein 1+; blood chemistry - BS 119 mg/dl, BUN 5 mg/dl, Cr 0.5 mg/dl; Na 139, K 5.7, Cl 103, HCO_3^- 21 mmol/l, Mg 2.1mg/dl, Ca 5.2 mg/dl, Zn 0.228 Ugm/dl; plasma ammonia 665, 526, 105 Umol/L respectively. Quantitative plasma amino acid analysis (Fig. 4) demonstrated initially marked elevation of citrulline 2,960 nmol/ml and glutamine 1,590 nmol/ml and came down to 1,500 nmol/ml and 600 nmol/ml respectively; urine sent to Japan for gas-liquid chromatography/mass spectrometry revealed orotic acid, characteristic of urea cycle disorders (Fig. 5). Subsequently, exchanged transfusions (x2), arginine 250 mg/kg/day, sodium benzoate 500 mg/kg/day, intravenous fluids with caloric intake between 80-120 cal/kg/day were given. She responded well and was rescued from hyperammonemic coma within 30 hours after aggressive treatment. She was given Product 80056 and regular formula which she tolerated well at protein 1 g/kg/day. She was discharged in good condition after 2 weeks. Her developmental assessment (DQ = 48) was at the level of moderate mental retardation at age 2 years when she returned to Bangkok in 2001 for a family visit.

DISCUSSION

The 5 reported cases of urea cycle disorders in 4 Thai infants and a Pakistani were collected over the past 8 years (1993 to 2001).

Argininosuccinic acid lyase deficiency (ALD) is the second most common enzymatic defect of the urea cycle. It is a rare autosomal recessive inborn error of metabolism. Deficiency of argininosuccinase results in accumulation of a large amount of argininosuccinic acid in blood, urine and cerebrospinal fluid. Marked hyperammonemia may occur and arginine deficiency occurs as a consequence of the metabolic block[10-12]. Outcome usually involves neurological and intellectual impairment in affected children. Impairments in the synthesis of urea lead to an accumulation of ammonium ions, which usually have a neurotoxic effect[13]. The most dramatic clinical presentation of UCD occurs

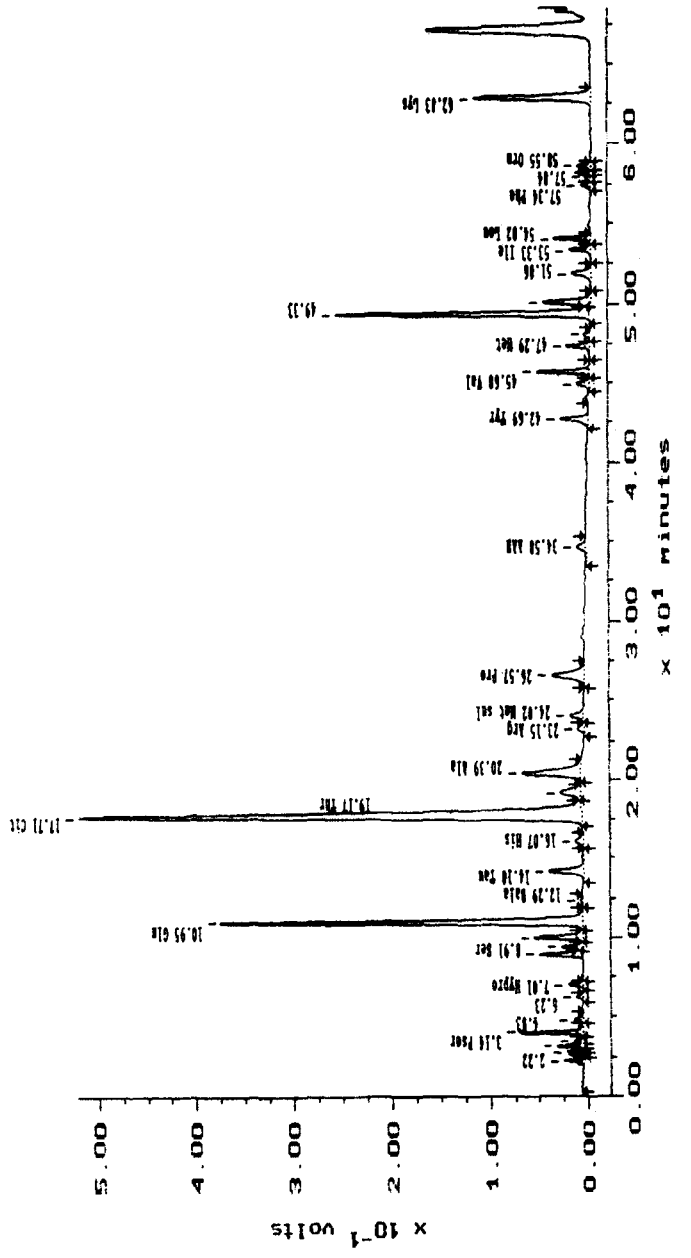

Fig. 4. Quantitative plasma amino acid analysis by high-performance liquid chromatography demonstrated markedly elevated plasma citrulline.

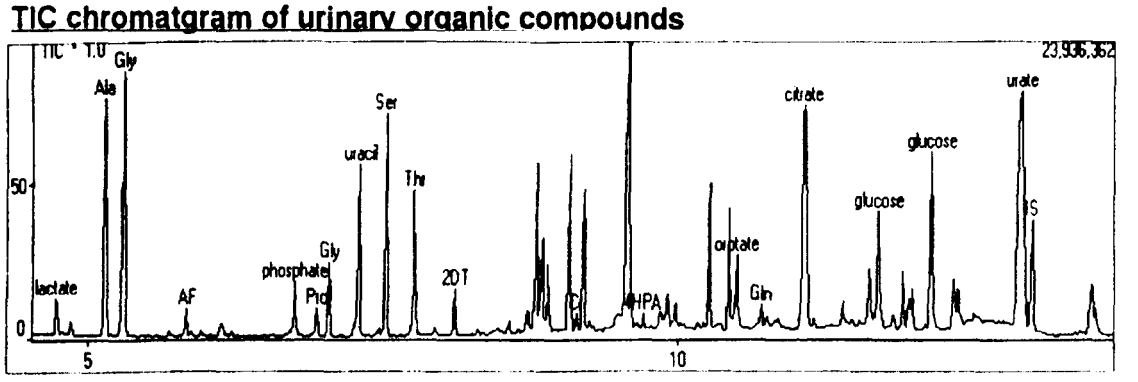

Fig. 5. Gas-liquid chromatography/mass spectrometry demonstrated urine orotic acid, characteristic of urea cycle disorder.

in full-term infants with no obstetric risk factors who appear normal for 24-48 h and then exhibit progressive lethargy, hypothermia and apnea all related to very high plasma ammonium levels[14,15].

One patient (case 1) was born in 1993 in Bangkok when urea cycle disorders (UCD) were not very well known among Thai pediatricians, due to the prevalence of infectious diseases in this part of the world. Inborn errors of metabolism (IEM) were taught in medical schools but physicians usually thought of IEM as rare diseases. Thus, they did not consider these UCDs in the differential diagnosis of very sick infants. Genetic consultation was made on the second episode of lethargy and coma. Moreover, very few laboratory facilities were able to perform reliable plasma ammonia, a very important clue to the diagnosis of UCDs. Therefore, the delayed diagnosis led to a very poor outcome in case 1. He is still alive, now 9 years old, and severely retarded.

As for case 2, who was born in Hat Yai Songkhla province in southern Thailand in year 2001; one observed again delayed diagnosis and lack of knowledge in the treatment of IEM, particularly UCDs. Referral to the tertiary care center was made only when the patient had already developed severe essential amino acid deficiency. Treatment of urea cycle disorders is considered an emergency procedure and consists of an immediate and long-term plan. The short-term or immediate treatment emphasizes elimination of hyperammonemia which causes cerebral edema, seizures, coma, mental retardation and neurological deficits[10]. The long-term treatment consists of limited protein intake, L-arginine free base and a mixture of essential amino acid to supply adequate caloric intake[11,12].

Ornithine transcarbamylase deficiency (OTC) is an X-linked inborn error of metabolism of the urea cycle which causes hyperammonemia and is treatable with supplemental dietary arginine and low-protein diet[16]. Russell et al (1962) described 2 cousins with chronic ammonia intoxication and mental deterioration. A defect is presumed to be present in urea synthesis at the level of conversion of ornithine to citrulline[17,18].

In case 3, this male infant who had neonatal-onset of urea cycle disorder developed severe neonatal hyperammonemia on day 5 after an episode of vomiting, poor feeding and later became lethargic, hypothermic and hyperventilation. Respiratory alkalosis and coma ensued requiring ventilatory support. The parents were counseled by a neonatalogist of the poor outcome; however, after two exchange transfusions the infant developed spontaneous respiration and was subsequently rescued from neonatal hyperammonemic coma. He did fairly well on sodium benzoate and sodium phenylacetate and arginine supplementation in the first 6 months. His developmental assessment (DQ) was 95. Despite attempts to maintain adequate nutrition with diet and arginine supplements he developed life-threatening and brain

damaging intercurrent hyperammonemia at age 10 months. Cerebral edema occurred with increased intracranial pressure and management became increasingly difficult. The parents were again counseled about the potentially poor outcome; they then requested no further therapeutic intervention and the infant soon succumbed. Only two months after his death his mother became pregnant again.

Another patient (case 4) was a sibling of case 3. The younger sib also developed similar symptoms and was diagnosed with OTC. He was referred to a tertiary care center on day 8 when he was already in a coma. The parents finally gave permission to discontinue all treatment after 2 weeks of aggressive treatment. These two cases of OTC were diagnosed early, however, the difficulty in management of urea cycle disorders, particularly the OTC showed the worst outcome. These two cases in male siblings also suggested that their mother must be the heterozygote for OTC. Molecular diagnosis is being done to confirm this assumption. Urea cycle defect is an inborn error of urea synthesis in which ammonium and other nitrogenous precursors of urea accumulate leading to episodic coma and a high mortality rate[19,20]. Therapy with peritoneal dialysis, essential amino acids or their nitrogen-free analogues has increased survival. Although life has been prolonged by these measures, long-term results have been discouraging with death usually occurring in the first year of life during an episode of hyperammonemic coma[21-24].

Citrullinemia is an inborn error of urea cycle metabolism caused by a deficiency of argininosuccinate synthetase (ASS), which catalyzes the condensation of citrulline and aspartate to form argininosuccinate. This results in a marked elevation in the concentrations of plasma citrulline and ammonia[25,26]. Clinical manifestation varies, ranging from a devastating metabolic derangement presenting with vomiting, convulsions, coma and death. Treatment consists of a low-protein diet, but has not been highly successful. It is an autosomal recessive disorder[27,28]. One patient (case 5) developed vomiting from day 6 and was not diagnosed until day 53 when she became stuporous and was referred to Siriraj Hospital when she was in coma. Elevation of plasma ammonia and citrulline in quantitative amino acid analysis confirmed the diagnosis of citrullinemia in this patient, the first such reported case in Thailand. The outcome of this patient was better than the others; she is now 2 years and 6 months old and her intellectual function is in the range of moderate mental retardation. Better outcome is possible if diagnosis is made sooner, since management has improved in the past several years.

SUMMARY

Inborn error of urea cycle disorders, has gained recognition among Thai pediatricians. Diagnosis and management of UCDs in Thailand have improved over the past several years. An important issue which needs to be emphasized is the rescue from neonatal hyperammonemic coma. Before attempting the rescue of a neonate with severe neonatal hyperammonemic encephalopathy, parents should be thoroughly counseled about the likely neurodevelopmental outcome. At present, there is no substitute for a physician who is keenly aware that all full-term neonates with nonspecific symptoms are candidates for symptomatic inborn errors of metabolism.

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โรคที่เกิดจากความผิดปกติของวงจรยูเรีย : รายงานผู้ป่วย 5 ราย†

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โรคที่เกิดจากความผิดปกติของวงจรยูเรียเป็นโรคพันธุกรรมเมตาบอลิคที่เกิดจากความผิดปกติของการสังเคราะห์ยูเรีย ซึ่งทำให้มีการสะสมของสารแอมโมเนียและสารตั้งต้นของยูเรีย นำไปสู่ภาวะ coma และมีอัตราการตายสูง การรักษาสามารถทำได้โดย peritoneal dialysis การให้กรดอะมิโนที่จำเป็นต่อร่างกายและสารอาหารที่ไม่มีไนโตรเจน จะนำไปสู่การรอดชีวิตได้ เรารายงานผู้ป่วย 5 รายที่เป็นโรคที่มีความผิดปกติของวงจรยูเรีย ซึ่งทุกรายมีภาวะแอมโมเนียสูงในเลือดและ coma แต่ได้รับการช่วยเหลือและรักษาจนผ่านพ้นภาวะ coma อย่างไรก็ดีผลลัพธ์ของผู้ป่วยแต่ละรายแตกต่างกันมาก

Argininosuccinate lyase deficiency (ALD) ผู้ป่วยรายแรกเป็นเด็กเพศชายอายุ 2 เดือน พ่อแม่เป็นลูกพี่ลูกน้องกัน จากจังหวัดสุพรรณบุรี เริ่มมีอาการไม่ดูดนมวันที่ 7 หลังคลอด เงื่องหงอย ชัก ตับโต และมีภาวะ respiratory alkalosis ต่อมามีภาวะระบบหายใจล้มเหลวและ coma พบระดับแอมโมเนียในเลือดสูงมาก ระดับ glutamic acid และ argininosuccinic acid และสาร anhydrides สูง จากการตรวจวิเคราะห์กรดอะมิโนนำไปสู่การยืนยันโรค ขณะนี้ผู้ป่วยมีอายุ 9 ปี และมีภาวะปัญญาอ่อนมาก ผู้ป่วยรายที่ 2 เป็นเด็กเพศชาย มีประวัติเงื่องหงอยและซึม ไม่ดูดนมในวันที่ 3 หลังคลอด ได้รับการรักษาแบบโรคติดเชื้อและจำเป็นต้องได้รับเครื่องช่วยหายใจประมาณ 6 วันจึงมีอาการดีขึ้น ต่อมาเข้ารับการรักษาในโรงพยาบาลอีกครั้งเมื่ออายุได้ 2 สัปดาห์ โดยมีอาการอาเจียน เซื่องซึม ชัก และระดับแอมโมเนียในเลือดสูง มีประวัติการแต่งงานในเครือญาติ ได้รับการส่งตัวมารักษาที่โรงพยาบาลศิริราชเมื่ออายุ 64 วัน โดยมีอาการขาดกรดอะมิโนที่จำเป็นอย่างรุนแรงและมี acrodermatitis enteropathica โดยมีระดับ citrulline สูงมากในเลือด ถึงแม้จะให้การรักษาอย่างเต็มที่ผู้ป่วยมีอาการติดเชื้อและเสียชีวิตเมื่ออายุ 78 วัน

Ornithine transcarbamylase deficiency (OTC) ผู้ป่วยรายที่ 3 เป็นเด็กเพศชาย อายุ 11 เดือน พ่อแม่ไม่เป็นญาติกัน มีอาการดูดนมได้น้อยเงื่องหงอยเมื่ออายุ 5 วัน ต่อมาอุณหภูมิร่างกายต่ำ ชัก หยุดหายใจและ coma ได้รับการช่วยเหลือออกมาจากภาวะ coma เมื่ออายุ 9 วันภายหลังให้การรักษาอย่างเต็มที่ แต่อย่างไรก็ดีผู้ป่วยเสียชีวิตเมื่ออายุ 11 เดือนจากอาการติดเชื้ออย่างรุนแรง ผู้ป่วยรายที่ 4 เป็นเด็กเพศชายและเป็นน้องชายของผู้ป่วยรายที่ 3 ซึ่งได้รับการส่งตัวมารับการรักษาที่โรงพยาบาลศิริราช เมื่ออายุได้ 8 วัน ด้วยภาวะระดับแอมโมเนียสูงในเลือดและ coma พ่อแม่ได้รับคำปรึกษาแนะนำทางพันธุศาสตร์โดยตลอดตั้งแต่มีลูกคนแรก (ผู้ป่วยรายที่ 3) แต่คู่สามีภรรยาตัดสินใจตั้งครรภ์ที่สองภายหลังลูกคนแรกเสียชีวิตได้เพียง 2 เดือน ผู้ป่วยเริ่มมีอาการอาเจียนและเซื่องซึมในวันที่ 2 หลังคลอด ต่อมาพบระดับแอมโมเนียสูงในเลือด ถึงแม้ได้การรักษาอย่างเต็มที่ผู้ป่วยมีภาวะแทรกซ้อนคือตับล้มเหลว ไตวาย และภาวะเลือดแข็งตัวเมื่ออายุ 15 วัน พ่อแม่ขอไม่รักษาอีกต่อไป ผู้ป่วยจึงเสียชีวิตเมื่ออายุได้ 18 วัน

Argininosuccinate synthetase deficiency (ASS) or Citrullinemia. ผู้ป่วยรายที่ 5 เป็นเด็กหญิงอายุ 7 สัปดาห์ เชื้อสายปากีสถาน พ่อแม่มีประวัติแต่งงานในเครือญาติ เริ่มมีอาการอาเจียนเป็นครั้งคราว ตั้งแต่อายุได้ 6 วัน การวินิจฉัยเบื้องต้นได้แก่ ruminations, sepsis และ pyloric stenosis ซึ่งผู้ป่วยได้รับการผ่าตัด อย่างไรก็ดีผู้ป่วยก็ยังมีอาการอาเจียน

ต่อไปและชัก พบระดับแอมโมเนียสูงในเลือดและ coma เมื่ออายุได้ 53 วัน ได้รับการช่วยเหลือออกจากภาวะ coma ภายในเวลา 30 ชั่วโมง พบระดับ citrulline และ L-glutamine สูงในเลือด ผู้ป่วยได้รับการรักษาจนอาการดีขึ้นและสามารถเดินทางกลับไปบ้านที่ Dubai ประเทศ United Arab Emirates ได้ภายใน 2 สัปดาห์

คำสำคัญ : โรคที่มีความผิดปกติของวงจรยูเรีย, ภาวะแอมโมเนียสูงในเลือด, ภาวะทางสมองที่มีสาเหตุทางเมตาบอลิค

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