Inherited Metabolic Disorders in Thailand†

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Abstract

The study of inborn errors of metabolism (IEM) in Thailand is in its infancy. The majority are clinically diagnosed since there are only a handful of clinicians and scientists with expertise in inherited metabolic disorders, shortage of well - equipped laboratory facilities and lack of governmental financial support. Genetic metabolic disorders are usually not considered a priority due to prevalence of infectious diseases and congenital infections. From a retrospective study at the Medical Genetics Unit, Department of Pediatrics, Siriraj Hospital; estimated pediatrics patients with suspected IEM were approximately 2-3 per cent of the total pediatric admissions of over 5,000 annually. After more than 10 years of research and accumulated clinical experiences, a genetic metabolic center is being established in collaboration with expert laboratories both in Bangkok (Chulabhorn Research Institute) and abroad (Japan and the United States). Numerous inherited metabolic disorders were identified - carbohydrate, amino acids, organic acids, mitochondrial fatty acid oxidation, peroxisomal, mucopolysaccharidoses etc.

This report includes the establishment of genetic metabolic center in Thailand, research and pilot studies in newborn screening in Thailand and a multicenter study from 5 institutions (Children's National Center, King Chulalongkorn Memorial Hospital, Pramongkutklao Hospital, Ramathibodi and Siriraj Hospitals). Inherited metabolic disorders reported are fructose-1, 6-bisphos-

phatase deficiency, phenylketonuria, homocystinuria, nonketotic hyperglycinemia, urea cycle defect (arginino succinate lyase deficiency, argininosuccinate synthetase deficiency), Menkes disease, propionic acidemia and mucopolysaccharidoses (Hurler, Hurler-Scheie).

Key word : Inherited Metabolic Disorders, Genetic Metabolic Center, Multicenter Study of Inherited Metabolic Disorders in Thailand

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The study of inborn errors of metabolism (IEM) in Thailand is in its infancy. The majority are clinically diagnosed since there are only a handful of clinicians and scientists with expertise in IEM, shortage of well - equipped laboratory facilities and lack of governmental financial support. Genetic metabolic disorders are usually not considered a priority due to prevalence of infectious diseases such as HIV and other congenital infections. From a retrospective study at the Medical Genetics Unit, Department of Pediatrics, Siriraj Hospital Faculty of Medicine from 1983-1988; the estimated pediatric patients with suspected IEM were approximately 2-3 per cent of the total pediatric admissions of over 5,000 annually. After more than 10 years (1987-2001) of research and accumulated clinical experiences, a genetic metabolic center is being established in collaboration with expert laboratories both in Bangkok (Chulabhorn Research Institute) and abroad (Japan and the United States).

IEM identified are : 1) *Carbohydrate disorders* - glycogen storage disorders - Pompe's (GSD type II), Von Gierke (GSD, Type I), Fructose-1, 6-bisphosphatase deficiency 2) *Amino acids disorders* - phenylketonuria, maple syrup urine disease, urea cycle disorders (argininosuccinate lyase deficiency, argininosuccinate synthetase deficiency and ornithine transcarbamylase deficiency), homocystinuria 3) *Organic acid disorders* - isovaleric acidemia (acute neonatal, chronic intermittent), methylmalonic acidemia, multiple carboxylase deficiency, alkaptonuria 4) *Mitochondrial Fatty Acid Oxidation disorders* - VLCAD, MCAD and carnitine deficiency 5) *Peroxisomal disorders* - rhizomelic chondrodysplasia punctata (RCDP), primary hyperoxaluria Type I, Zellweger syndrome 6) *Lipidosis* - Niemann - Pick (NPD) Type A, Gaucher, GM_1 Gangliosidosis and Sandhoff disease 7) *Mucopolysaccharidosis* (MPS) - Hurler, Hunter, Scheie, Morquio, Maroteaux-Lamy, SanFillipo and Sly syndrome 8) *Disorders of Purine metabolism* - Lesch-Nyhan[1].

Establishment of Genetic Metabolic Project / Center in Thailand

A research project, "Inborn errors of metabolism in Asian Countries" was organized by Professor Isamu Matsumoto in May 1998 using gas chromatography - mass spectrometry (GC/MS) demonstrated numerous inherited metabolic disease in high - risk neonates and infants in India, China and Thailand. The result clearly demonstrated that the prevalence of IEM is higher than previously

recognized. From this collaboration and funding from Siriraj Hospital's new Chaofa - Maha Chakri Building led to the establishment of the *Genetic Metabolic Center* at the Medical Genetics Unit, Department of Pediatrics, Siriraj Hospital in 2001. The first GC/MS of its kind to be used for diagnosis of IEM in Thailand was supported by JICA (Japan Intergovernmental Cooperation Agency). Expertise in GC/MS technology was transferred to Thai scientists by Japanese experts, Dr. Toshihiro Shinka and Dr. Kenji Hara[2,3].

Newborn Screening in Thailand

As for newborn screening, pilot projects for screening congenital hypothyroidism (CH) and phenylketonuria (PKU) was initiated at Siriraj Hospital (with assistance from the JICA training program in Sapporo) and only CH in other university hospitals (Chulalongkorn and Ramathibodi) 1993. At present, neonatal screening for CH and PKU have been done in Thailand by the Ministry of Public Health since 1995, with approximately 40 per cent coverage. The 3rd Asia-Pacific Regional Meeting of the International Society for Neonatal Screening (Professor Hiroshi Naruse as President of ISNS) was organized in Chiang Mai, Thailand in 1998; followed by establishment of the Neonatal Screen Society of Thailand[4,5].

During the Fourth Asia-Pacific Regional meeting of the International Society on Neonatal Screen (ISNS) recently held in Manila, the Philippines from October 17-19, 2001; Charoensiriwatana W et al from the Ministry of Public Health reported that a newborn screening program will be implemented as routine practice for all public health sectors for CH and PKU by the year 2002. So far, 1,425,025 newborn babies in Thailand have already been screened (from 1996-2000) and the incidence of CH and PKU was reported to be 1:3,314 and 1:285,005 respectively. An expanded newborn screening program to include CAH, G6PD deficiency, MSUD is being considered at Siriraj Hospital Faculty of Medicine in the near future.

Multicenter study of IEMs in Thailand

More recently, a multicenter study of IEM was performed by a group of Thai pediatric geneticists from 4 medical schools (Chulalongkorn, Pramongkutklao, Ramathibodi and Siriraj) and Children's National Center in Bangkok. The results are shown in Table 1.

CASE REPORTS

1. Fructose-1, 6-Bisphosphatase deficiency (FBP_1) Hereditary fructose 1, 6-bisphosphatase deficiency is characterized by episodic spells of

Table 1. IEMs in Thai hospitals. (1988-2001)

Disorders	Children's	Chulalongkorn	Pramongkutklao	Ramathibodi	Siriraj
Carbohydrate dis.					
Galactosemia	1	-	-	-	-
Glycogen storage dis.					
GSD, Type I	-	-	-	-	1
GSD, Type II	-	-	2	-	3
GSD, Type III	-	-	1	-	-
Fructose 1, 6-biphosphatase def	-	-	-	-	1
Amino acid dis.					
PKU	7	-	-	-	2
Hyperphenylalaninemia	10	-	-	-	-
Tyrosinemia, Type I	1	1	-	-	1
MSUD	4	-	1	2	5
Homocystinuria	-	-	-	-	2
Albinism	-	-	1	-	2
NKH	-	-	-	1	4
Urea Cycle dis.					
ALD	-	-	-	-	2
OTC	-	-	-	-	2
ASD	-	-	-	-	1
Unidentified UCD	1	-	-	2	-

Table 1. IEMs in Thai hospitals (continue). (1988-2001)

Disorders	Children's	Chulalongkorn	Pramongkutklao	Ramathibodi	Siriraj
Organic acid dis.					
IVA	-	-	-	-	4
MMA	-	1	-	-	2
PA	1	1	-	-	-
Alkaptonuria	-	-	-	-	1
Multiple carboxylase deficiency (MCD)	1	1	-	-	1
Mitochondrial dis.					
MCAD	-	-	-	-	1
Translocase def	-	-	-	-	1
Carnitine deficiency	-	-	-	-	1
Peroxisomal dis.					
RCDP	-	-	-	-	2
Zellweger	-	-	-	-	-
Primary hyperoxaluria, Type I	-	-	-	-	2
Lipidosis					
Niemann-Pick, Type I	-	-	-	-	2
Gaucher	-	2	-	-	10+
Sandhoff	-	-	-	-	1
GM1 gangliosidosis	-	-	1	-	1
Mucopolysaccharidosis					
Hurler	-	1	-	-	2
Hurler-Scheie	-	-	-	-	1
Scheie	-	-	-	-	1
Hunter	-	1	-	3	10
SanFillippo	-	-	-	-	2
Morquio	-	1	-	-	3
Maroteaux-Lamy	-	-	-	-	1
Sly	-	-	-	-	1
Unidentified MPS	-	-	7	-	5
Dis. of Purine Metabolism					
Lesch-Nyhan	-	-	-	-	1
Dis. of Copper Transport					
Menkes	-	-	1	2	1
Leucodystrophies					
X-ALD	-	1	-	2	-
Others	-	1	5	-	8
Others					
Lipoprotein lipase def	-	-	1	-	-
Hyperlipoproteinemia	-	-	1	-	-
Porphyria	-	1	-	-	2
Cystinuria	-	1	-	-	-
Methhemoglobinuria	-	1	-	-	-
HMG CoA lyase def	-	1	-	-	-

hyperventilation, apnea, hypoglycemia, ketosis and lactic acidosis, with a precipitous and often lethal course in the newborn infant. Later episodes are often triggered by fasting and febrile illness. Gluconeogenesis is severely impaired(6).

The authors report a 2 year 3 month old boy (S.S.) who was referred with chief complaint of severe vomiting, lethargy 4 days prior to admission. History of recurrent vomiting required at least 10 previous hospitalizations which improved upon receiving intravenous fluids and correction of severe metabolic acidosis (HCO^-_3<10) plasma with bicarbonate. Semicomatose condition and marked hepatomegaly but no hypoglycemia were observed upon admission to the intensive care unit. Quantitative plasma amino acids analysis was normal; however, urine organic acid analysis *via* gas-liquid chromatography and mass spectrometry (GC/MS) demonstrated increased excretion of lactate, 3-hydroxybutyrate (3HB), glycerol, glycerol-3-phosphate (G3P),

markers compounds of fructose-1, 6-diphosphatase deficiency (FDPD) were found in the urine. This is most likely the first reported case of FBP1 in Thailand.

2. Phenylketonuria (PKU) is due to a deficiency of phenylalanine hydroxylase (PAH) and is inherited as an autosomal recessive trait. It is characterized chemically by the excretion of large amounts of phenylpyruvic acid, clinically by mental retardation, seizures, hypopigmentation, microcephaly, mousy odor, eczema, neonatal vomiting and defective myelin formation[7].

(K.K.) This 2 year old male infant with observed hypopigmentation and seizures since age 5 and 9 months respectively, was referred to Siriraj Hospital at age 1 year 11 months due to delayed development. Although consanguinity was denied, both parents came from the same village in Khon Kaen province. Hyperphenylalanine 1165.14 μmmol/L (normal 50-100 μmmol/L), positive urine $FeCl_3$ were noted and urine for organic acids analysis *via* (gas liquid chromatography and mass spectrometry) demonstrated increased excretion of 2-OH- phenylalanine, phenylalanine and 4-OH-phenyllactate. Developmental assessment (DQ = 39) was consistent with severe mental retardation. He was treated with low-phenylalanine diet (Lofenalac) which reduced his seizure activities satisfactorily.

3. Homocystinuria due to cystathionine β-synthase deficiency is characterized by increased plasma homocystine and methionine. The cardinal manifestations develop in the ocular, skeletal, cardiovascular and central nervous system. Ectopia lentis, marfanoid habitus, restricted joint mobility, thromboembolism and mental retardation are common, but highly variable manifestations (McKusick, 1972). Vitamin B_6 - responders are often mildly affected. The inheritance is autosomal recessive[8].

The authors report 2 siblings with a history of parental consanguinity and diagnoses of homocystinuria. **Case 1.** (W.J.), (Fig. 1) A nine-year-old girl had ectopia lentis, marfanoid habitus, positive urine cyanide nitroprusside and mild mental retardation. Quantitative amino acid analysis demonstrated elevated plasma methionine and homocysteine. **Case 2.** A six-year-old girl also had positive urine cyanide nitroprusside, elevated plasma methionine and homocysteine with borderline intelligence. The first case of homocysteine in Thailand was reported in 1980,

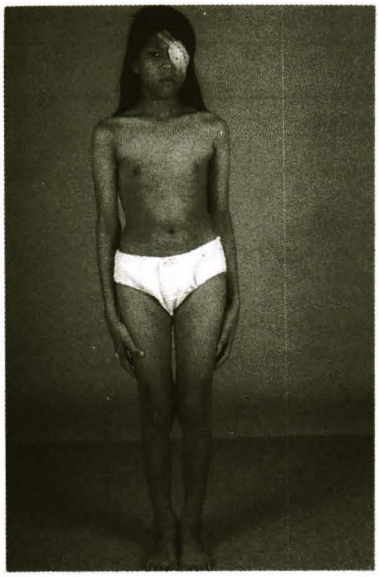

Fig. 1. Nine-year-old girl with homocystinuria.

by Cholvibul P et al, Air Force Med J 1980 ; 26 : 171-8. This is most likely the second reported case in twenty years. Management included Vit B_6, methionine - restricted diet and genetic counseling. Enzyme assay and DNA analysis are being studied.

4. Nonketotic hyperglycinemia (NKH) is an inborn error of glycine degradation in which large quantities of glycine accumulate in all body tissues, including the central nervous system. The neonatal phenotype presents with lethargy, hypotonia and myoclonic jerks and progressing to apnea and often death. Intractable seizures and profound mental retardation is common in this disorder. Glycine is a neurotransmitter and is excitatory in the cortex at the N-methyl-D-aspartate receptor channel complex. The diagnosis is established at the substrate level by simultaneously determining CSF and plasma glycine concentrations and calculating CSF : plasma glycine ratio. NKH is inherited as autosomal recessive trait[9].

(P.V.) This 2 year-9 month-old infant girl developed vomiting after the first few days of life. Delayed development, microcephaly and recurrent vomiting were observed at age 3 months. Siriraj Hospital investigation at 10 months revealed CSF and plasma glycine ratio greater than 0.08. Abnor-

mal electroencephalogram and magnetic resonance imaging were demonstrated. Treatment consisted of sodium benzoate, folic acid, low-protein diet, L-carnitine and dextrometorphan. Poor outcome and prognosis were observed.

5. Urea Cycle Defect (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(10).

5.1 Argininosuccinate lyase deficiency (ALD) (W.S.) A 3 month old male infant, a product of a consanguineous marriage (Songkhla province); developed poor feedings on day 3-lethargy, poor sucking, convulsion, hepatomegaly and subsequently hyperammonemic coma ; referred to Siriraj Hospital at 3 months with essential amino acid deficiency and severe dermatitis (acrodermatitis enteropathica). Citrullinemia and increased glutamic acid and argininosuccinic acid and its anhydrides in the urine confirmed the diagnosis of ALD. He expired at 5 months of age of overwhelming sepsis, fungemia and renal insufficiency.

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

6. Menkes Disease - an X-linked disorder resulting in severe growth failure and profound neurodegeneration in early childhood, caused by a defect in copper absorption. Clinical features usually present by 3 months of age by loss of developmental milestones and failure to thrive. A typical appearing infant usually has a cherubic face with pudgy cheeks, sagging jowls and scant eyebrows. Hair is sparse, resembling steel wool and on microscopy reveals twisting of hair shaft (pilli torti) as well as fractures and longitudinal splitting. Diagnosis is usually difficult in the neonatal period until the more typical signs and symptoms appear(11).

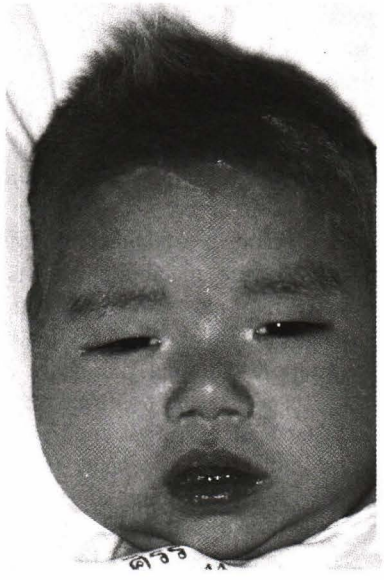

Fig. 2. Four-month-old boy with Menkes disease.

(P.C.), (Fig. 2) A 4-month-old boy with seizures from the age of 3 months, later hypotonia and delayed development were observed. There was no parental consanguinity. Initial diagnosis was albinism, phenylketonuria due to hypopigmented hair and skin. Computed tomography of the brain demonstrated diffuse demyelination. Generalized cortical cerbellar atrophy was found on magnetic resonance imaging of the brain. Quantitative plasma amino acids and urine organic acids analyses were within normal limits; however, low serum copper and ceruloplasmin were noted. Trichorrhexis nodosa was later demonstrated. A trial of copper sulfate treatment was given for one month without any demonstrable improvement and copper histidine was not available.

7. Propionic Acidemia (PA). Isolated deficiency of propionyl CoA carboxylase, a major cause of the ketotic hyperglycinemia syndrome, results in the accumulation of propionate in blood and of 3-hydroxy-propionate, methylcitrate, tiglylglycine and unusual ketone bodies in urine. It is characterized by severe metabolic ketoacidosis, which often appears

in the neonatal period and requires vigorous alkali therapy and protein restriction. Clinical course is characterized by repeated relapses, usually precipitated by excessive protein intake, constipation, or intercurrent infection. Treatment has been quite difficult and neurologic sequelae have been common[12].

(S.B.) A one year and 5 months old boy with a history of severe, metabolic acidosis since day 1, subsequently required respiratory support for 9 days; recurrent vomiting and lethargy led to repeated respiratory support. Clinical diagnosis of organic acidemia was suspected and confirmed by 2 months of age. Increased excretion of methylcitrate, propionylglycine and 3-OH-propionate found in urine *via* gas-liquid chromatography and mass spectrometry. Inadequate treatment due to unavailability of carnitine caused numerous hospitalizations, growth failure and delayed development. Subsequently treated at Siriraj Hospital at 1 year and 5 months with restricted protein intake, carnitine, biotin and control of infections with satisfactory outcome and guarded prognosis.

8. Mucopolysaccharidosis (MPS) - a heterogeneous group of lysosomal storage disorders caused by deficiency of enzymes catalizing the stepwise degradation of glycosaminoglycans (mucopolysaccharides). There are 10 known enzymes deficiencies that give rise to six distinct MPS. Stepwise degradation of glycosaminoglycans requires 4 glycosidases, 5 sulfatases and 1 nonhydrolytic transferase. Clinical features are chronic and progressive with multisystem involvement, organomegaly, dyostosis multiplex and abnormal facies. Genetic transmission usually is autosomal recessive, except MPS II which is X-linked. Definite diagnosis of MPS is established by enzyme assays[13].

8.1 Hurler syndrome (MPS I-H) Deficiency of α-L-iduronidase results in a wide range of clinical involvement, with 3 major recognized clinical entities-Hurler, Scheie and Hurler-Scheie-syndromes. MPS I-H is the most severe end of the spectrum. A progressive disorder with multiple organ and tissue involvement leading to premature death usually by 10 years of age. Diagnosis is usually made between 6-24 months of age - hepatosplenomegaly, skeletal deformities, coarse facial features, enlarged tongue, prominent forehead and joint stiffness. Progressive cloudy cornea since first year of life.

Hurler syndrome MPS I–H (S.P.) A 2-year-10 month-old girl, product of a non-consanguinous marriage who developed normally until age 6 months when she developed frequent upper respiratory tract infections. Clinical diagnosis of MPS I-H was made at one year of age with positive urine mucopolysaccharides. Clinical features consisted of short stature, coarse facies, cloudy cornea, dysostosis multiplex congenita and mental retardation. Confirmation by enzyme diagnosis was performed at Siriraj Hospital in collaboration with Chulabhorn Research Institute. Bone marrow transplantation was considered; however, due to HLA incompatibility in a normal sibling, it was not done.

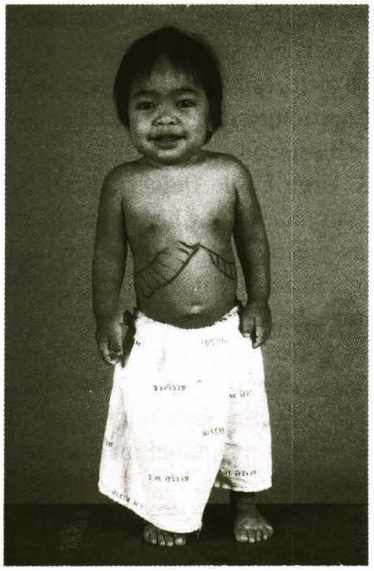

Fig. 3. Two-year and 2-month-old girl with Hurler syndrome (MPS I-H).

Hurler syndrome MPS I–H (P.N.), (Fig. 3) A 2-year-2 month-old girl with coarse facies, cloudy cornea, claw- hand deformity, hepatosplenomegaly and generalized contracture of wrist, elbow, knee joints. Delayed growth and development (DQ 69) and urine positive for mucopolysaccharidoses were observed. Consanguinity was denied. Recurrent upper respiratory tract infections, noisy breathing, persistent copious nasal discharge, characteristic "dysostosis multiplex" and hearing loss were also observed. Enzyme confirmation is being done.

Hurler-Scheie syndrome (MPS I H/S) - (C.K.), (Fig. 4) A 4 year-5 months-old boy with onset of short stature and joint stiffness since age 2. Initially seen by orthopedics for joint limita-

tions; however, coarse facies, short stature, macrocephaly, claw-hand deformities, mild cloudy cornea, umbilical hernia, mild scoliosis, hepatosplenomegaly, positive urine mucopolysaccharides and normal intelligence (DQ 98) were observed with a clinical phenotype that is intermediate between Hurler and Scheie syndromes. Enzyme analysis was performed (Chulabhorn Research Institute, Bangkok) to check for α-L-iduronidase deficiency.

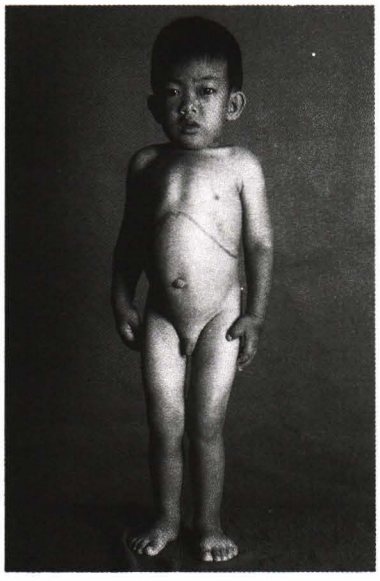

Fig. 4. Four-year and 5-month-old boy with Hurler-Scheie syndrome (MPS I H/S).

SUMMARY

1. Due to marked improvement in health care in Thailand, inherited disorders are increasingly being recognized. There has been increased awareness and knowledge among health professionals particularly Thai pediatricians in the past decade.

2. A Genetic Metabolic Project/Center has been established at Division of Medical Genetics, Department of Pediatrics, Siriraj Hospital since the year 2000 with assistance from JICA - Japanese Intergovernmental Cooperation Agency which provided a Gas-Liquid Chromatography and Mass Spectrometry (GC/MS) and funding from Chaofa-Maha Chakri Pediatric Building at Siriraj Hospital (HPLC). Tandem Mass Spectrometry technology will be introduced in Thailand in the near future.

3. National neonatal screening program has been implemented into the public health infrastructure since 1996, providing approximately 40 per cent coverage at present. Plans are being made to accomplish 100 per cent coverage in year 2002.

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REFERENCES

1. Wasant P, Liammongkolkul S, Srisomsap C, Svasti J, Naylor EW, Matsumoto I. Inherited metabolic disorders in Thailand-Siriraj experience: Proceedings, 3rd Asia-Pacific Regional Meeting of the International Society of Neonatal Screen. Southeast Asian J Trop Med Public Health 1999; (30 Suppl 2): 124 -37.
2. Wasant P, Matsumoto I, Liammongkolkul S. Detection of inborn errors of metabolism in Thai infants *via* gas chromatography and mass spectrometry: Proceedings, 3rd Asia-Pacific Regional Meeting of the International Society of Neonatal Screen. Southeast Asian J Trop Med Public Health 1999; (30 Suppl 2): 160-5.
3. Wasant P, Naylor EW, Liammongkolkul S. Detection of inherited metabolic disorders *via* tandem mass spectrometry in Thai infants ; Proceedings, 3rd Asia-Pacific Regional Meeting of the International Society of Neonatal Screen. Southeast Asian J Trop Med Public Health 1999; (30 Suppl 2): 138-9.
4. Wasant P, Liammongkolkul S, Srisawat C, et al. Neonatal screening for congenital hypothyroidism and phenylketonuria at Siriraj Hospital, Mahidol University, Bangkok, Thailand-A pilot study: Proceedings, 3rd Asia-Pacific Regional Meeting of the International Society of Neonatal Screen. Southeast Asian J Trop Med Public Health 1999; (30 Suppl 2): 33-7.
5. Naruse H. Establishment of screening systems in East Asia ; Proceedings, 3rd Asia-Pacific Regional Meeting of the International Society of Neonatal Screen. Southeast Asian J Trop Med Public Health 1999; (30 Suppl 2): 5-10.
6. Gitzelman R, Steinmann B, van den Berghe G. Disorders of fructose metabolism. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 1489-520.
7. Scriver CR, Kaufman S. Hyperphenylalaninemia: Phenylalanine hydroxylase deficiency. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 1667-724.
8. Mudd SH, Levy HL, Kraus JP. Disorders of Transsulfuration. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 2007-56.
9. Hamosh A, Johnston MV. Nonketotic Hyperglycinemia. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 2065-78.
10. Brusilow SW, Horwich AL. Urea cycle enzymes. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 1909-63.
11. Culotta VC, Gitlin JD. Disorders of copper transport. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 3105-26.
12. Fenton WA, Gravel RA, Rosenblatt DS. Disorders of propionate and methylmalonate metabolism. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 2165-93.
13. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In : Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease, 8th edition, New York: McGraw-Hill, 2001: 3421-52.

โรคพันธุกรรมเมตาบอลิคในประเทศไทย†

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การศึกษาโรคพันธุกรรมเมตาบอลิคในประเทศไทยยังอยู่ในระยะแรกเริ่ม โรคส่วนใหญ่วินิจฉัยได้ทางคลินิก เนื่องจากขาดแคลนผู้เชี่ยวชาญและนักวิทยาศาสตร์ รวมทั้งห้องปฏิบัติการที่มีความสามารถในการวินิจฉัยและวิเคราะห์โรคกลุ่มนี้ซึ่งจัดว่ามีความยุ่งยากมาก นอกจากนั้นยังไม่ได้รับการสนับสนุนอย่างจริงจัง เนื่องจากแพทย์ยังมีความเชื่อว่าโรคพันธุกรรมเมตาบอลิคเป็นโรคที่พบได้น้อย จากการศึกษาย้อนหลังของหน่วยเวชพันธุศาสตร์ ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล (ปี พ.ศ. 2526-2531) พบว่าผู้ป่วยที่สงสัยเป็นโรคพันธุกรรมเมตาบอลิคมีประมาณร้อยละ 2-3 ของผู้ป่วยที่เข้ารับการรักษาในภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล (ซึ่งมีทั้งหมดประมาณปีละ 5,000 กว่าคน)

ในระยะ 10 กว่าปีที่ผ่านมานี้ (พ.ศ. 2531-2544) การศึกษาวิจัยและประสบการณ์ในการดูแลรักษา ผู้ป่วยโรคพันธุกรรมเมตาบอลิคเพิ่มพูนมากขึ้นและได้นำไปสู่การก่อตั้งศูนย์พันธุกรรมเมตาบอลิค โดยมีการร่วมมือกับสถาบันในประเทศ (สถาบันวิจัยจุฬาภรณ์) และต่างประเทศ (ญี่ปุ่นและสหรัฐอเมริกา) สามารถวินิจฉัยโรคพันธุกรรมเมตาบอลิคได้หลากหลาย เช่นโรคที่เกิดจากความผิดปกติของ carbohydrates, amino acids, organic acids, mitochondrial fatty acid oxidation, peroxisomal, lipidosis และ mucopolysaccharidoses เป็นต้น การศึกษานี้กล่าวถึงการก่อตั้งศูนย์พันธุกรรมเมตาบอลิคในประเทศไทย งานวิจัยที่เกี่ยวกับการตรวจกรองทารกแรกเกิดและการรวบรวมผู้ป่วยจาก 5 สถาบัน ได้แก่ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี, โรงพยาบาลจุฬาลงกรณ์, วิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี และคณะแพทยศาสตร์ศิริราชพยาบาล โรคพันธุกรรมเมตาบอลิคที่ได้รายงานไว้ในการศึกษานี้ได้แก่ fructose-1, 6-bisphosphatase deficiency, phenylketonuria, homocystinuria, nonketotic hyperglycinemia, urea cycle defect (arginino succinate lyase deficiency, argininosuccinate synthetase deficiency), Menkes disease, propionic acidemia และ mucopolysaccharidoses (Hurler, Hurler-Scheie) เป็นต้น

คำสำคัญ : โรคพันธุกรรมเมตาบอลิค, ศูนย์พันธุกรรมเมตาบอลิค, Multicenter Study of Inherited Metabolic Disorders in Thailand

พรสวรรค์ วสันต์, ชิษณุสรร สวัสดิวัตน์,
จันทรกานต์ ศรีสมทรัพย์, สมพร เหลี่ยมมงคลกุล
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