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Amino acid disorders detected by quantitative amino acid HPLC analysis in Thailand: An eight-year experience

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ABSTRACT

Background: Amino acid disorders are a major group of inborn errors of metabolism (IEM) with variable clinical presentations. This study was aimed to provide the data of amino acid disorders detected in high-risk Thai patients referred to our metabolic lab from all over the country.
Methods: From 2001 to 2009, we analyzed amino acids by HPLC in 1214 plasma and cerebrospinal fluid specimens. These specimens were obtained from patients with clinical suspicion of IEM or with positive newborn screening. The clinical data of the patients with confirmed diagnoses of amino acid disorders were also analyzed.
Results: Fifty-eight patients were diagnosed with amino acid disorders, including 20 cases (34.5%) with maple syrup urine disease, 13 (22.4%) with phenylketonuria and hyperphenylalaninemia, 13 (22.4%) with nonketotic hyperglycinemia, 9 (15.5%) with urea cycle defects, 2 (3.4%) with classical homocystinuria, and 1 (1.7%) with ornithine aminotransferase deficiency. There was considerable delay in diagnoses which led to poor outcomes in most patients.
Conclusion: The prevalence of amino acid disorders in Thailand is distinct from other countries. This will guide the selection of the prevalent IEM for the future expansion of newborn screening program in this country.

1. Introduction

Amino acids are the primary components of proteins, and they are involved in several cellular metabolic pathways. The inborn errors of amino acid metabolism are a group of genetic disorders in which an enzyme deficiency results in the accumulation of amino acids. Phenylketonuria (PKU) was discovered in 1934 as the first inborn error of amino acid metabolism that resulted in mental retardation [1]. Thereafter, several amino acid disorders have been identified, such as maple syrup urine disease (MSUD), urea cycle defects (UCD), tyrosinemia, homocystinuria, and nonketotic hyperglycinemia (NKH). Clinical presentation of patients with amino acid disorders is often non-specific and suggestive of a variety of non-genetic conditions, which result in underdiagnosis. With the advancement of biochemical methods for detecting amino acids in physiological fluids, amino acid disorders can now be diagnosed and patients can be treated promptly to prevent morbidity and mortality. An amino acid analysis is performed by either ion exchange or high-performance liquid chromatography (HPLC) [2].

At our institute, we have provided metabolic tests, including urine organic acids and plasma amino acids, on patient specimens sent from all over the country. Previously, we have reported Thai patients with organic acid disorders detected by urine gas chromatography/mass spectrometry (GC/MS) [3].

2. Materials and methods

2.1. Materials

Our laboratory received a total of 1214 plasma and cerebrospinal fluid (CSF) specimens of patients with clinical suspicion of IEM from July 2001 to December 2009. The clinical findings of these patients included lethargy, poor feeding, persistent vomiting, intractable seizures, unexplained neurological deficits, developmental delay, recurrent coma, neurodegeneration, unexplained liver dysfunction or cholestasis, skin and hair changes, and ophthalmologic

Abbreviations: ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; CPS1, carbamoylphosphate synthetase I; HCY, homocystinuria; HPA, hyperphenylalaninemia; HPLC, high-performance liquid chromatography; IEM, inborn error of metabolism; MSUD, maple syrup urine disease; NAGS, N-acetyl glutamate synthetase; NKH, nonketotic hyperglycinemia; OAT, ornithine aminotransferase; OTC, ornithine transcarbamylase; PKU, phenylketonuria; PTPS, 6-pyruvoyltetrahydropterin synthase.

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findings suggestive of IEM. The abnormal laboratory findings included persistent/recurrent hypoglycemia, metabolic acidosis with increased anion gap, hyperammonemia, cytopenia, imaging suggestive of IEM, and abnormal newborn screening for PKU. The study was approved by the ethics committee of the Faculty of Medicine Siriraj Hospital, Mahidol University.

2.2. Amino acid analyses

The heparinized blood specimens were collected from the patients for plasma amino acid analyses. The CSF specimens were collected at the same time of plasma collection in the cases with suspected NKH. Sample preparation, derivatization, and amino acid separation by HPLC were performed following the protocol described by Svasti et al. [4]. The targeted amino acids included phosphoserine, aspartic acid, glutamic acid, α-aminoadipic acid, hydroxyproline, phosphoethanolamine, serine, asparagine, glycine, glutamine, taurine, histidine, citrulline, threonine, alanine, arginine, proline, α-aminobutyrate, tyrosine, valine, methionine, isoleucine, leucine, phenylalanine, tryptophan, ornithine, and lysine. The results of other metabolic tests including urine organic acids analyzed by GC/MS, plasma homocysteine, and a biopterin assay were also reviewed.

3. Results

3.1. Clinical data

From our laboratory record, a total of 58 patients from 54 families with amino acid disorders were diagnosed by either plasma or CSF amino acid analyses. The following amino acid disorders were excluded: tyrosinemia due to a large number of false-positive cases from transient tyrosinemia in newborns or liver dysfunctions, and histidinemia due to its benign course. There were 20 cases (34.5%) with MSUD, 13 (22.4%) with PKU and hyperphenylalaninemia (HPA), 13 (22.4%) with NKH, 9 (15.5%) with UCD, 2 (3.4%) with classical homocystinuria, and 1 (1.7%) with ornithine aminotransferase (OAT) deficiency. Among the 9 cases with UCD, 7 cases had citrullinemia type I, and 2 cases had carbamoylphosphate synthetase I (CPS1) or N-acetyl glutamate synthetase (NAGS) deficiency. For analyzing the clinical data, we only reviewed patients who were referred and treated at our hospital (Table 1). Among the 32 families, 18 families (56%) had a history of consanguinity or inbreeding, and 17 families (53%) were from the northeastern region of Thailand. Most of the clinical onsets in this study, after exclusion of the cases identified by newborn screening for PKU, were within the neonatal period (22 out of 28 cases, 79%) presenting with either neonatal encephalopathy or

Table 1
Clinical data of 33 cases with amino acid disorders.

Case no.	Sex	Regional origin	Age at presentation	Age at diagnosis	Consanguinity or inbreeding	Diagnosis	Clinical presentations	Other findings	Age at last follow-up	Outcome
1	M	Central	6 d	1 mo	–	Classical MSUD	Neonatal encephalopathy	–	13 y	Severe MR
2	M	Northeast	5 d	3 mo	+	Classical MSUD	Neonatal encephalopathy	–	3 y	Severe MR
3	M	Northeast	5 d	3 mo	+	Classical MSUD	Neonatal encephalopathy	Pancreatitis	2 y	Dead
4	F	Northeast	4 d	5 mo	+	Classical MSUD	Neonatal encephalopathy	–	8 mo	Severe MR
5	F	Central	3 d	2 mo	+	Classical MSUD	Neonatal encephalopathy	–	6 y	Severe MR
6	F	Central	4 d	2 mo	+	Classical MSUD	Neonatal encephalopathy	–	8 mo	Severe MR
7	F	Central	6 d	11 d	+	Classical MSUD	Neonatal encephalopathy	–	4 y	Dead
8	F	Northeast	2 d	3 mo	+	Classical MSUD	Neonatal encephalopathy	–	3 y	Severe MR
9	F	Northeast	3 d	2 mo	+	Classical MSUD	Neonatal encephalopathy	–	11 mo	Dead
10	M	South	8 d	21 d	+	Classical MSUD	Neonatal encephalopathy	–	2 mo	Dead
11	F	Northeast	7 d	3 mo	+	Classical MSUD	Neonatal encephalopathy	–	12 mo	Severe MR
12	M	Northeast	1 d	4 mo	+	NKH	Neonatal seizures	–	4 y	Severe MR
13	F	South	3 mo	2 y	–	NKH	Infantile seizures	Hyperammonemia	11 y	Dead
14	F	Northeast	1 d	3 d	+	NKH	Neonatal seizures	–	2 y	Dead
15	F	Central	2 d	5 d	+	NKH	Neonatal seizures	–	12 d	Dead
16	F	Northeast	2 d	3 d	+	NKH	Neonatal seizures	–	5 d	Dead
17	F	South	5 y	5 y	–	Late-onset NKH	Seizures, spastic quadriparesis	Choreoathetoid movements	6 y	Mild MR
18	M	Northeast	5 mo	2 y	+	Classical PKU	Seizures, DD	Hypopigmentation	3 y	Severe MR
19	M	Central	NBS	12 d	–	Classical PKU	Newborn screen	–	4 y	Normal DQ
20	M	South	NBS	2 mo	+	Classical PKU	Newborn screen	Poor compliance to treatment	15 m	Mild delay
21	M	Northeast	NBS	2 mo	–	HPA	Newborn screen	–	4 y	Normal DQ
22	F	Central	NBS	10 d	–	HPA	Newborn screen	–	12 m	Normal DQ
23[a]	F	Central	NBS	1 mo	–	PTPS deficiency	Dystonia	Confirmed by biopterin assay	3 y	Normal DQ
24	F	Central	9 y	10 y	+	Classical HCY	Lens subluxation	Marfanoid habitus	20 y	Mild MR
25[b]	F	Central	6 y	6 y	+	Classical HCY	Lens subluxation	Marfanoid habitus	17 y	Borderline MR
26	M	Northeast	7 d	28 d	–	Citrullinemia I	Neonatal encephalopathy	–	6 mo	Dead
27	M	Northeast	2 d	18 d	–	Citrullinemia I	Neonatal encephalopathy	–	6 mo	Dead
28	F	Central	10 d	3 mo	–	Citrullinemia I	Neonatal encephalopathy	–	6 y	Borderline MR
29	F	Northeast	12 d	14 d	–	Citrullinemia I	Neonatal encephalopathy	–	4 y	Normal DQ
30	F	Pakistan	6 d	2 mo	+	Citrullinemia I	Neonatal encephalopathy	–	10 y	Severe MR
31	M	North	10 d	5 mo	–	CPS1/NAGS def.	Neonatal encephalopathy	–	3 y	Dead
32	M	Northeast	5 d	22 d	–	CPS1/NAGS def.	Neonatal encephalopathy	–	10 m	Dead
33	M	Central	5 y	21 y	–	OAT def.	Gyrate atrophy of choroid and retina	–	26 y	Normal IQ

M, male; F, female; d, day(s); mo, month(s); y, year(s); NBS, newborn screening; MSUD, maple syrup urine disease; NKH, nonketotic hyperglycinemia; PKU, phenylketonuria; HPA, hyperphenylalaninemia; PTPS, 6-pyruvoyltetrahydropterin synthase; HCY, homocystinuria; CPS1, carbamoylphosphate synthetase I; NAGS, N-acetyl glutamate synthetase; OAT, ornithine aminotransferase; DD, developmental delay; MR, mental retardation; DQ, developmental quotient; IQ, intelligence quotient.

[a] Case 23 has been reported by Vatanavicharn et al. [5].

[b] Case 25 is a younger sibling of case 24.

seizures. However, there was considerable delay in diagnoses, and only 10 out of 22 cases were diagnosed by 1 month of age. Twenty-two cases (67%), including the patients with MSUD, neonatal-onset NKH, classical PKU (born before the newborn screening program implemented), and most UCD, had poor outcomes with either death or severe mental retardation. The better outcomes with mild mental retardation to normal intelligence were found in 11 patients (33%) including: late-onset NKH, PKU/HPA (detected by newborn screening), homocystinuria, citrullinemia type I (2 out of 5 cases), and OAT deficiency.

3.2. Amino acid results

The amino acid levels of the patients with amino acid disorders are tabulated and compared with the normal reference ranges in Table 2. We excluded the amino acid profiles of 2 cases with MSUD because they were intensively treated at other hospitals before specimens were collected. The amino acid profiles of all MSUD cases showed marked elevations of branched-chain amino acids especially leucine, decreased alanine, and increased leucine/alanine molar ratios. Not all of the NKH cases had hyperglycinemia. There were three NKH cases, including one case with the late-onset type, who had plasma glycine within the reference range. Among the PKU/HPA cases, 5 cases had phenylalanine levels consistent with classical PKU ($\geq$1200 μmol/l), 5 cases consistent with mild PKU (>600 and <1200 μmol/l), and 3 cases consistent with mild HPA ($\leq$600 μmol/l). The HPA case caused by 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency had a phenylalanine level of 1006 μmol/l within the range of mild PKU. The cases with citrullinemia type I were diagnosed by markedly increased plasma citrulline and glutamine, as well as absence of argininosuccinate in the urine organic acids. All citrullinemia type I cases had decreased arginine, except for case No.29, who was detected early, and had mild phenotype. The cases with CPS1 or NAGS deficiency were diagnosed by markedly increased glutamine and low citrulline, as well as absence of orotate in the urine organic acids. The enzymatic or molecular analysis to distinguish between two disorders has not been performed. For the siblings with classical homocystinuria, both of them had markedly increased methionine in the plasma amino acids, as well as markedly increased plasma total homocysteine (240 and 234 μmol/l, normal 2.2–7.5 μmol/l).

4. Discussion

In recent years, there have been considerable advances in the development of diagnostic tests of IEM, such as tandem mass spectrometry (MS/MS) [9]. However, analysis of amino acids in the physiological fluids by HPLC or ion exchange is still an indispensable diagnostic work-up. In this study, we could diagnose 58 cases with amino acid disorders. From our previous study of IEM in Thailand from 1997 to 2001, we could diagnose 17 cases with amino acid disorders in which MSUD was the most common (6 out of 17 cases, 35%) [10]. The newborn screening program for PKU in Thailand was implemented around year 2000, and the number of identified PKU and HPA cases increased from one case in the previous study to 13 cases in the present study. Nevertheless, MSUD was still the most prevalent amino acid disorders in this study. This suggests that MSUD could be the most common amino acid disorder in Thailand. This remarkably contrasts with the other IEM studies from several countries (Table 3), in which PKU and HPA are the most prevalent disorders. MSUD is very rare in the western countries with a frequency of 1 in 185,000 based on routine screening data [18] except for Mennonite people in Pennsylvania with a birth incidence of 1 in 380 due to the founder effect [19]. The high frequency of MSUD has also been reported in Filipino population in which 40% came from the province of Pampanga in the northern part of the Philippines [20]. This also could be explained by the founder mutation in the dihydrolipoyl transacylase gene (E2) [21]. Interestingly, 4 out of 11 MSUD cases (36%) in this study were from Sisaket province in the northeastern region of Thailand. A founder effect or other genetic explanations for the high prevalence of MSUD in this population are being investigated. The predominant disorder of UCD in our study is citrullinemia type I in contrast to those from the western countries in which ornithine transcarbamylase (OTC) deficiency is predominant [22].

More than half of the patients with amino acid disorders in this study were from the northeastern region of Thailand even though only approximately 30% of Thai population resided in this region

Table 2
The abnormal amino acids in plasma and CSF of the affected cases.

Disease	N (%) (Total = 56)	Abnormal amino acids in plasma	Concentration (Mean ± SD μmol/l)	Minimum–Maximum (μmol/l)	Reference range for age (μmol/l)[a]
MSUD	18 (32.1%)	Leucine	2103.4 ± 597.8	1234.9–3562.4	42.1–133.2
		Isoleucine	331.1 ± 123.7	76.0–530.8	15.2–74.9
		Valine	491.8 ± 218.7	80.7–922.3	73.7–273.2
		Alanine	68.0 ± 54.0	9.42–206.4	149.9–565.0
		Leu/Ala ratio	62.9 ± 63.6	9.72–241.0	0.12–0.53[b]
NKH	13 (23.2%)	Glycine	842.8 ± 530.0	221.0–2039.4	94.1–463.0 (0–6 mo) 107.9–319.1 (3–6 y)
		Glycine (CSF)	189.6 ± 129.8	20.4–469.2	<10[c]
		CSF: plasma Gly ratio	0.24 ± 0.14	0.11–0.56	<0.04[c]
PKU or HPA	13 (23.2%)	Phenylalanine	1032.7 ± 409.0	215.1–1524.7	25.0–74.9
		Tyrosine	59.5 ± 16.4	32.8–93.1	30.5–139.0
		Phe/Tyr ratio	18.6 ± 8.6	4.7–30.7	<3[d]
Citrullinemia type I	7 (12.5%)	Glutamine	3727.5 ± 3526.2	396.9–9614.5	52.4–727.7
		Citrulline	1641.2 ± 896.5	700.1–2599.4	0–108.1
		Arginine	19.8 ± 16.2	0–47.8	24.4–106.7
CPS1/NAGS def.	2 (3.6%)	Glutamine	970.7 ± 88.0	908.5–1032.9	52.4–727.7
		Citrulline	4.9 ± 2.7	3.0–6.9	0–108.1
		Arginine	28.0 ± 8.8	21.8–34.2	24.4–106.7
Classical HCY	2 (3.6%)	Methionine	967.7 ± 89.4	904.5–1030.9	9.8–43.9
OAT def.	1 (1.8%)	Ornithine	603.0	603.0	19.6–70.5

MSUD, maple syrup urine disease; NKH, nonketotic hyperglycinemia; PKU, phenylketonuria; HPA, hyperphenylalaninemia; CPS1, carbamoylphosphate synthetase I; NAGS, N-acetyl glutamate synthetase; HCY, homocystinuria; OAT, ornithine aminotransferase; Leu, leucine; Ala, alanine; Gly, glycine; CSF, cerebrospinal fluid.

[a] From Svasti et al. [4].
[b] From Morton et al. [6].
[c] From Applegarth and Toone [7].
[d] From Walter et al. 8].

Table 3
Amino acid disorders detected in selective screening of IEM in distinct populations.[a]

Amino acid disorders[b]	San Diego, USA (3 years)	Freiburg, Germany (17 years)	British Columbia, Canada (27 years)	Kuwait (3 years)	Singapore (13 years)	Southern India (2 years)[c]	Shanghai, China (5 years)[c]	Thailand (present study) (8 years)
PKU and HPA	15 (33.3%)	24 (20.2%)	198 (81.1%)	10 (37.0%)	6 (17.1%)	19 (34.5%)	21 (29.2%)	13 (22.4%)
MSUD	7 (15.6%)	14 (11.8%)	2 (0.8%)	1 (3.7%)	4 (11.4%)	11 (20.0%)	7 (9.7%)	20 (34.5%)
NKH	8 (17.8%)	43 (36.1%)	18 (7.4%)	7 (26.0%)	3 (8.6%)	6 (10.9%)	3 (4.2%)	13 (22.4%)
Homocystinuria	3 (6.7%)	1 (0.8%)	6 (2.5%)	5 (18.5%)	2 (5.8%)	1 (1.8%)	–	2 (3.5%)
Hyperornithinemia	1 (2.2%)	3 (2.5%)	2 (0.8%)	–	6 (17.1%)	7 (12.7%)	–	1 (1.7%)
CPS/NAGS deficiency	–	–	3 (1.2%)	–	–	–	5 (6.9%)	2 (3.5%)
OTC deficiency	5 (11.1%)	17 (14.3%)	9 (3.7%)	–	7 (20%)	–	7 (9.7%)	–
ASS deficiency	6 (13.3%)	10 (8.4%)	3 (1.2%)	4 (14.8%)	6 (17.1%)	5 (9.0%)	–	7 (12.0%)
ASL deficiency	–	5 (4.2%)	3 (1.2%)	–	1 (2.9%)	–	–	–
Arginase deficiency	–	2 (1.7%)	–	–	–	6 (10.9%)	4 (5.6%)	–
Citrin deficiency	–	–	–	–	–	–	25 (34.7%)	–

PKU, phenylketonuria; HPA, hyperphenylalaninemia; MSUD, maple syrup urine disease; NKH, nonketotic hyperglycinemia; CPS1, carbamoylphosphate synthetase I; NAGS, N-acetyl glutamate synthetase; OTC, ornithine transcarbamylase; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase.

[a] Data were reviewed from various studies: USA [11], Germany [12], Canada [13], Kuwait [14], Singapore [15], India [16], China [17].

[b] Tyrosinemia and histidinemia were not included.

[c] The studies from Southern India and Shanghai used tandem mass spectrometry for selective screening of IEM.

[23]. The high prevalence of amino acid disorders in this region could be explained by high rates of consanguinity and inbreeding which are related to poverty, isolated rural villages, and local traditions. The majority of the patients in this study had unfavorable outcomes due to delayed diagnoses and limitations in obtaining special formulas and medications. Currently, only congenital hypothyroidism and PKU/HPA are screened, and funded by the Thai government [24]. The data from this study will guide the future expansion of newborn screening for IEM in Thailand. In our study, MSUD was the most common amino acid disorder. Therefore, MSUD should be considered for expanded newborn screening by MS/MS. However, most of our MSUD cases developed the symptoms within 7 days of life, before any newborn screening result would be available. But the benefit of newborn screening for MSUD still exists. For example, the nonspecific symptoms of MSUD generally result in delayed diagnosis, but with positive results of MSUD screening, the patients could be diagnosed and treated promptly. This will provide the same benefit for urea cycle defects, organic acidemias, and fatty acid oxidation disorders.

In conclusion, our study indicates that amino acid analysis by HPLC could diagnose several amino acid disorders in the high-risk patients. Early detection and timely diagnosis could lead to favorable outcomes. Expanded newborn screening by MS/MS can provide this opportunity. Nevertheless, its cost-benefit must be evaluated thoroughly especially in developing countries with budget limitations.

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References

[1] Folling A. Ueber Ausscheidung von Phenylbrenztraubensaeure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillitaet. Z Physiol Chem 1934;227:169–76.
[2] Duran M. Amino acids. In: Blau N, Duran M, Gibson KM, editors. Laboratory guide to the methods in biochemical genetics. Heidelberg: Springer-Verlag; 2008. p. 53–90.
[3] Wasant P, Liammongkolkul S, Kuptanon C, Vatanavicharn N, Sathienkijakanchai A, Shinka T. Organic acid disorders detected by urine organic acid analysis: twelve cases in Thailand over three-year experience. Clin Chim Acta 2008;392:63–8.
[4] Svasti J, Wasant P, Tiensuwan M, et al. Normal plasma free amino acid levels in Thai children. J Med Assoc Thai 2001;84:1558–68.
[5] Vatanavicharn N, Kuptanon C, Liammongkolkul S, et al. Novel mutation affecting the pterin-binding site of PTS gene and review of PTS mutations in Thai patients with 6-pyruvoyltetrahydropterin synthase deficiency. J Inherit Metab Dis 2009, doi:10.1007/s10545-009-1221-x [Online publication].
[6] Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelly RI. Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics 2002;109:999–1008.
[7] Applegarth DA, Toone JR. Nonketotic hyperglycinemia (glycine encephalopathy): laboratory diagnosis. Mol Genet Metab 2001;74:139–46.
[8] Walter JH, Lee PJ, Burgard P. Hyperphenylalaninemia. In: Fernandes J, Saudubray JM, van den Berghe G, Walter JH, editors. Inborn metabolic diseases. fourth edition. Heidelberg: Springer-Verlag; 2006. p. 222–32.
[9] Schulze A, Lindner M, Kohlmüller D, Olgemöller K, Mayatepek E, Hoffmann GF. Expanded newborn screening for inborn errors of metabolism by electrospray ionization-tandem mass spectrometry: results, outcome, and implications. Pediatrics 2003;111:1399–406.
[10] Wasant P, Vatanavicharn N, Srisomsap C, Sawangareetrakul P, Liammongkolkul S, Svasti J. Retrospective study of patients with suspected inborn errors of metabolism at Siriraj Hospital, Bangkok, Thailand (1997–2001). J Med Assoc Thai 2005;88:746–53.
[11] Borden M. Screening for metabolic disorders. In: Nyhan NL, editor. Amino acid metabolism in clinical medicine. Norwalk: Appleton-Century-Crofts; 1984. p. 401.
[12] Lehnert W. Long-term results of selective screening for inborn errors of metabolism. Eur J Pediatr 1994;153:S9–S13.
[13] Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969–1996. Pediatrics 2000;105:e10.
[14] Yadav GC, Reavey PC. Aminoacidopathies: a review of 3 years experience of investigations in a Kuwait hospital. J Inherit Metab Dis 1988;11:277–84.
[15] Tan IK, Gjra B, Lim MS. Study of inherited metabolic disorders in Singapore — 13 years experience. Ann Acad Med Singapore 2006;35:804–13.
[16] Nagaraja D, Mamatha SN, De T, Christopher R. Screening for inborn errors of metabolism using automated electrospray tandem mass spectrometry: study in high-risk Indian population. Clin Biochem 2010;43:581–8.
[17] Sun W, Wang Y, Yang Y, et al. The screening of inborn errors of metabolism in sick Chinese infants by tandem mass spectrometry and gas chromatography/mass spectrometry. Clin Chim Acta 2011;412:1270–4.
[18] Chuang DT, Shih VE. Maple syrup urine disease (branched-chain ketoaciduria). In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. eighth edition. New York: McGraw-Hill; 2001. p. 1971–2006.
[19] Puffenberger EG. Genetic heritage of the Old Order Mennonites of southeastern Pennsylvania. Am J Med Genet C Semin Med Genet 2003;121C:18–31.
[20] Lee JY, Chiong MA, Estrada SC, Cutiongco-De la Paz EM, Silao CL, Padilla CD. Maple syrup urine disease (MSUD)—clinical profile of 47 Filipino patients. J Inherit Metab Dis 2008;31(Suppl. 2):281–5.
[21] Silao CL, Padilla CD, Matsuo M. A novel deletion creating a new terminal exon of the dihydrolipoyl transacylase gene is a founder mutation of Filipino maple syrup urine disease. Mol Genet Metab 2004;81:100–4.
[22] Brusilow S, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, therapy. In: Barness LA, DeVivo DC, Kaback MM, Morrow G, Oski FA, Rudolph AM, editors. Advances in pediatrics. Chicago: Mosby; 1996. p. 127.
[23] National Statistics Office. 100th anniversary of population censuses in Thailand: population and housing census 2010: 11th census of Thailand. Available from URL http://popcensus.nso.go.th/en [accessed on Mar 4, 2012].
[24] Charoensiriwatana W, Janejai N, Boonwanich W, Krasao P, Chaisomchit S, Waiyasilp S. Neonatal screening program in Thailand. Southeast Asian J Trop Med Public Health 2003;34(Suppl. 3):94–100.