DETECTION OF PHENYLKETONURIA BY THE NEWBORN SCREENING PROGRAM IN THAILAND

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Abstract. This study evaluated the newborn screening program for phenylketonuria (PKU) in Thailand from 1996 to 2006. During the study period, 5,243,841 newborns were screened, of which16 were confirmed to have PKU. The phenylalanine levels ranged from 20.30-30.68 mg/dl (mean 25.82 mg/dl). All the patients who were diagnosed through the newborn screening program had normal growth and development after treatment except for 2 cases who were subsequently found to have a 6-pyruvoyltetrahydropterin synthase deficiency. Four additional cases of PKU diagnosed were siblings of screening detected cases who all presented with mental retardation, microcephaly, hypopigmented hair and skin and seizures in one case. Although these patients were treated with a phenylalanine restricted diet, all of them had moderate to severe psychomotor retardation. The results of this study confirm the benefit of early detection and treatment of PKU through the screening program.

INTRODUCTION

Phenylketonuria (PKU) is caused by phenylalanine hydroxylase deficiency characterized by elevated plasma levels of phenylalanine and its metabolites. In untreated cases, there is gradual development of irreversible severe mental retardation, seizures, microcephaly and hypopigmented hair and skin (Nyhan and Ozand, 1998; Scriver and Kaufman, 2001; Smith and Lee, 2001; Rezvani, 2007). Infants with PKU appear normal at birth. Diagnosis of PKU by clinical criteria is usually made later when the infant is a few months old after the development of irreversible brain damage (Matalon and Michals, 1991; Rezvani, 2007). The clinical manifestations of classic phenylketonuria are rarely reported now in developed countries where newborn screening is widespread (Yalaz *et al*, 2006). Newborn screening has allowed early detection and successful treatment with a low phenylalanine diet (Levy, 1986; Seashore, 1990; Smith *et al*, 1991; RMRCWP, 1993; NIH, 2001; Therrell and Adams, 2007). In the present study, the authors describe 18 cases of classic PKU and 2 cases of 6-pyruvoyltetrahydropterin synthase deficiency in Thai infants.

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MATERIALS AND METHODS

Medical records of all patients diagnosed as having PKU by newborn screening between October 1996 and September 2006 were reviewed. Information regarding the subjects was obtained, including demo-

graphic data, birth weight, gender, gestational age and a history of consanguineous marriage. Blood samples for screening were obtained from infants from all provinces in Thailand. The specimens were collected on filter paper and tested using the Guthrie method and/or the fluorometric method by the Department of Medical Sciences. All the positive cases were referred to the Queen Sirikit National Institute of Child Health for confirmation of the diagnosis and treatment. Confirmatory testing was done by plasma amino acid analysis using high performance liquid chromatography. The diagnosis of classic PKU was given when the blood phenylalanine level was equal to or greater than 20 mg/dl (1,200 μmole/l) and urinary pterins were normal. Laboratory data and information regarding the clinical course and management were analysed. Descriptive statistics were used for data analysis.

RESULTS

A total of 5,243,841 newborns were screened by the Department of Medical Sciences, Ministry of Public Health between October 1996 and September 2006. Sixteen cases of PKU (Nos.1-16) were identified through the newborn screening program. Four older subjects (Nos.17-20), siblings of screening detected cases, were born before the nationwide screening program was introduced. Clinical profiles of the 20 cases are shown in Table 1. There were 13 males and 7 females. All cases were born at term after an unevenful pregnancy. The mean birth weight was 2.9 kg, (range 2.2-3.5 kg). All were in good condition at birth. Four patients were from northern Thailand, 5 patients were from northeastern Thailand, 7 patients were from central Thailand and 4 patients were from southern Thailand. The 20 patients came from 15 families, 10 families each having one child with PKU, 5 families each having two children with PKU. Consanguineous marriage was found in one family (No. 8). Laboratory investigation confirmed that 18 patients had classic PKU and 2 children had 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency. The mean phenylalanine level was 25.82 mg/dl, (range 20.30-30.68 mg/dl). Urinary pterin analysis in 2 cases (Nos.8 and 13) affected with PTPS deficiency revealed the urinary biopterin and total biopterin (B%) were very low and the urinary neopterin was very high, consistent with PTPS deficiency.

DISCUSSION

Newborn screening for PKU was started in Thailand in 1996 by the Department of Medical Sciences, Ministry of Public Health. At present, a nationwide program which covers newborns around the country has been established. During the study period 20 cases of PKU were detected. Sixteen cases were detected by the newborn screening program and 4 cases were found in siblings of screening positive cases. The incidence of PKU was 1:327,740. The incidence of PKU in other countries ranges from 1:10,000 to 1:70,000 (AAP, 1996; Aoki, 2003; Jiang *et al*, 2003). The incidence of PKU in Thailand is lower than the worldwide incidence; it is a rare disease in Thailand.

Treatment of PKU with a low phenylalanine diet has been used since 1953 (Bickel *et al*, 1953). The benefits of early treatment in ameliorating the clinical course of PKU are well established, especially if they are treated before one month of age (Williamson *et al*, 1981). Sixteen cases of PKU (Nos.1-16) were identified through the newborn screening program, twelve of them (75%) came for treatment after the age of one month. They were started on treatment with a low phenylalanine diet at age between 25 and 108 days (mean 59 days). This delay was caused by

Table 1
Clinical profile of 20 children with PKU.

Case no.	Sex	Birth weight (kg)	Penylalanine level (mg/dl)	Age at treatment onset (days)	History of siblings affected with PKU	Urinary pterins
1	M	3.1	24.41	78	-	Normal
2	F	3.4	32.20	62	-	Normal
3	M	3.5	27.70	108	-	Normal
4	M	3.5	30.68	55	+	Normal
5	M	3.5	30.58	107	+	Normal
6	M	3.2	26.33	74	-	Normal
7	F	2.5	24.48	96	+	Normal
8	M	2.5	25.23	25	-	Abnormal
9	M	2.9	25.30	53	-	Normal
10	M	2.6	20.70	38	+	Normal
11	M	2.2	27.10	38	-	Normal
12	F	2.7	30.30	26	-	Normal
13	M	2.7	23.40	68	-	Abnormal
14	F	2.7	25.50	67	+	Normal
15	F	2.9	24.50	26	-	Normal
16	M	2.7	20.30	30	-	Normal
17	M	3.0	27.20	5 years	-	Normal
18	F	2.8	24.14	12 years	-	Normal
19	F	3.5	23.28	8 years	-	Normal
20	M	3.0	23.10	9 years	-	Normal

many factors such as a delay in retesting and confirmation of the initial results, difficulty in tracing patients because of inaccurate addresses or lack of telephones or living in remote rural areas where transportation is a problem. After dietary modification, all patients showed normal growth and development except for 2 cases (Nos. 8 and 13) who were later found to have PTPS deficiency. The first case of PTPS deficiency (No. 8) was diagnosed because he developed progressive cerebral deterioration despite an early neonatal diagnosis of hyperphenylalaninemia and effective dietary control. The diagnosis of PTPS deficiency was made at age 5 months. The second case (No.13) was detected by urinary screening for pterin levels. Both cases received treatment with neurotransmitters (L-dopa/carbidopa, 5-hydroxytrytophan) in addition to a phenylalanine restricted diet and showed a positive response. These 2 infants were diagnosed rather late because the screening for tetrahydrobiopterin (BH_4) deficiency is not an integral part of newborn screening in Thailand. Dietary compliance was poor in most PKU patients. A major problem was government funding covered only diagnostic examinations, a phenylalanine restricted diet is not widely available in Thailand. Another reason was inadequate parental compliance with diet control because of their apparently normal children. As a consequence, the phenylalanine levels of the majority patients were not within the target range for appropriately treated patients.

Four additional PKU cases not diagnosed by the national newborn screening program were included in the study. All of them were siblings of neonates with PKU detected at birth by the screening program. They all appeared normal at birth and then gradually had delayed development, microcephaly, light-colored hair and learning problems. One case also developed eczema, seizures and behavior abnormalities. Unfortunately, screening for PKU had not yet started when they were born. All of them had been diagnosed previously with mental retardation of unknown etiology.

PKU is inherited as an autosomal recessive trait, the recurrent risk for the next child is 1 in 4. From the present study, consanguineous marriage was found in one family and siblings affected with PKU were found in 5 families. Therefore, genetic counseling is very important and should be provided for all families.

In conclusion, the newborn screening program is beneficial for the early detection and treatment of PKU, especially in the prevention of mental retardation. PKU patients not detected by newborn screening are easily missed and can be diagnosed as having delayed development of unknown etiology. Screening for BH_4 deficiencies should be carried out in each hyperphenylalaninemic infant.

ACKNOWLEDGEMENTS

The authors would like to thank the Department of Medical Sciences, Ministry of Public Health; Queen Sirikit National lnstitute of Child Health; Chulabhorn Research Institute; Dr Kwang-Jen Hsiao, Director, Genome Research Center, National Yang-Ming University, Taipei, Taiwan for their help and laboratory support. We would like to thank the Children's Hospital Foundation and Mead Johnson Nutritional Products (Thailand) for providing the special diet for these patients.

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