The initiation and progress of phenylketonuria programmes in China

RG Chen

The incidence of phenylketonuria in mainland China is similar to that of the West and various estimates include 1:17 000, 1:16 500 and 1:11 186. The exact incidence in China in different regions still has to be clarified. Affected neonates appear normal at birth, with dark hair at birth and vomiting is rare. In infancy and childhood, the fair complexion becomes conspicuous. Head circumference is related to the degree of mental development. We have also observed a "phenylketonuria-like syndrome." These children are mentally retarded with fair complexion but do not have elevated blood phenylalanine levels or urinary ketones. The chances of a second child suffering from this abnormality in 75 high-risk families was found to be 1:3. For treatment, we suggest a low-phenylalanine diet for at least for five years and longer, if possible. Gene analysis has revealed differences in the frequency and composition of mutations in northern and southern Chinese patients.

HKMJ 1996;2:

Key words: Phenylketonuria; Phenylalanine hydroxylase deficiency; Neonatal screening

Introduction

Investigations into phenylketonuria (PKU) in China have been conducted only over the past 14 years. This work has progressed from surveys through management, to prenatal diagnosis. This paper reviews the work that has been done.

Incidence

I did not expect to see many cases of PKU in China when I first began a pilot, neonatal, screening programme in Shanghai in 1982. Identification of the first case in 1982 and two cases in 1983 made me believe that screening for PKU in neonates was a necessary preventive measure, and the screening has become routine in my laboratory since then. There are now three laboratories involved in Shanghai that screen the city's neonatal population. Based on our seven years of experience in which 21 cases of PKU have been identified (of 358 767 newborns in Shanghai), the incidence in Shanghai has been estimated to be 1:17 000.[1]

Another screening programme organised by the Beijing Medical University's Department of Pediatrics involved 11 provinces and cities and 198 320 newborns in obstetric departments were screened. Classical PKU was detected in 10 neonates and hyperphenylalaninemia in two, which gives an overall incidence of 1:16 500.[2] A third set of data from a collaborative study sponsored by WHO and the Ministry of Public Health, from 1992 to 1993, involved seven cities and yielded an incidence of 1:11 186 (Table).

From the three data sets, it can be seen that the incidence of PKU in China is similar to that reported in the West. Because the number of neonates screened is low (the number screened represents only 1% to 2% of the babies born), and the diversity of ethnic groups in China, the exact incidence of PKU in different regions and ethnic groups still has to be clarified. The impression that the incidence of PKU is lower in southern China than it is in the north, needs to be confirmed by further screening.

Diagnosis and differential diagnosis

Clinically, the hair of PKU babies at birth is dark and turns light only after three to four months. Vomiting, as mentioned in textbooks, is rare and usually not severe, if present. The fair complexion of

Shanghai Institute for Pediatric Research, Shanghai Second Medical University, Shanghai, China
RG Chen, MD

Correspondence to : Dr RG Chen

Table. The results of neonatal screening for phenylketonuria in seven cities in China

Cities	No. screened	No. identified (Incidence)
Beijing	50 015	7
Shanghai	89 040	7
Tianjing	13 262	5
Shenyang	22 024	0
Jinan	8 828	0
Guangzhou	41 600	2
Chengdu	10 140	0
Total	**234 909**	**21 (1/11 186)**

these children is obvious to a clinician. The characteristic musty smell is usually overlooked by parents because they are used to it, but it is easily noticed by visitors. In untreated patients, microcephaly is common and the circumference of the head correlates with the degree of mental development. Convulsions, especially in the form of infantile spasm, with characteristic electroencephalogram findings are common. The general physical examination is usually normal but some may have spastic cerebral palsy. Many of the parents (obligatory heterozygotes) have a fair complexion.

Of interest to the differential diagnosis, are those cases with mental retardation and fair complexion, but without elevated blood phenylalanine levels or the presence of ketones in the urine. Pedigree studies have shown autosomal recessive characteristics. Similar cases have been seen in other clinics in China. Possibly, this represents a new disease entity that warrants further investigation. I refer to this as the "PKU-like syndrome."

Of the 546 PKU patients (male:female ratio, 337:209) seen in our clinic, only 64 (8.5%) were identified through population neonatal screening. Of these cases, 29 (22%) were from high-risk families. And in the 75 high-risk families in our series, 25 (33%) had a second child with the disease. In two families, three siblings had PKU. We often use these examples to advise parents not to have a second child, unless a prenatal diagnosis is to be performed when a second pregnancy occurs.

Management

For the management of the disease, work on the production of a low-phenylalanine diet was undertaken. After five years, a prescription was finalised and production commenced in 1987. Much support was obtained from Dr Naruse of Japan and Dr Guthrie of the United States for the realisation of this endeavour. This product is based on the removal of phenylalanine from acid hydrolysed casein.[3] In addition, a new low-phenylalanine product has recently been successfully developed in Beijing. This product is a mixture of different amino acids minus phenylalanine with the addition of low-phenylalanine starch. Patients are placed on a restricted diet for at least five years or more.

Two families with maternal PKU syndrome were seen in our clinic, emphasising the importance of educating treated female PKU patients. Five cases of hyperphenylalaninemia, defined as blood phenylalanine levels consistently above 4 mg/dL and below 20 mg/dL have been reported and followed by the author.[4] Phenylalanine loading tests were conducted in three patients. The blood phenylalanine levels at 1, 2, and 4 hours after loading (0.1 g/kg, given orally) were all above normal, indicating an error in phenylalanine metabolism. After follow up, three cases with blood phenylalanine levels of 4-10 mg/dL and one case with blood phenylalanine of 16 mg/dL were found to have normal IQs while another case with blood phenylalanine levels not higher than 12 mg/dL showed retarded psychomotor development. We suggest that a hyperphenylalaninemic child with blood phenylalanine above 10 mg/dL should be under close supervision and on a low-phenylalanine diet.

Tetrahydrobiopterin (BH4) deficiency is recognised as a malignant hyperphenylalaninemic condition. In our PKU follow up clinic, we have diagnosed six cases of BH4 deficiency in four families. The first case was suspected because of the patient's continuing deteriorating general condition, especially muscular weakness, despite the successful lowering of the blood phenylalanine level. Diagnosis was confirmed by a urinary biopterin profile.[5] All six were specified as having synthetase deficiency. Only two of these patients are still alive and one is being treated with BH4 provided by Dr Hsiao, of Taiwan. This patient has a 6-pyruvoyl-tetrahydropterin synthetase (PTPS) deficiency, confirmed by mutation analysis of the PTPS cDNA (data not shown). We now routinely screen for BH4 deficiency in all new PKU cases. To my knowledge, there are three more BH4 deficiency patients in China, one each from Beijing, Tianjin, and Guangzhou.

Genetic and prenatal diagnosis

The human phenylalanine hydroxylase (PAH) locus is located on the 12q22-24.1 region of chromosome 12. The length of the PAH gene is approximately 90 Kb including 13 exons and 12 introns encoding an approximately 2.4 Kb length of mature mRNA. According to the data of mutation analysis of 30 PKU families from northern China, Arg243Gln (23.3%) and Arg413Pro (10.0%) were the two most frequent mutations in this region.[6] In our laboratory, we analysed exon 7 of the PAH gene in 58 PKU patients from southern China and five mutations were identified. One of the mutations, IVS6nt-1, has not been reported previously in the world literature. The Arg243Gln change only constituted 9.5%.[7] These results indicate that there are differences in the frequencies and composition of mutations between the northern and southern regions of China.

Prenatal diagnosis has been successfully performed in 16 high-risk pregnancies in Beijing. Five foetuses predicted to be affected were ended by induced abortion.[8]

In summary, the coverage of neonatal screening for PKU is still low in China, treatment for PKU is expensive, prenatal diagnosis is complex and expensive, and knowledge about PKU among general practitioners is lacking. All of these factors have made the service to PKU patients inadequate.

References

1. Chen RG, Pan XS, Qian DL, Guo H. Twenty-one cases of phenylketonuria out of 358 767 newborns in Shanghai, China. J Inherit Metab Dis 1989;12:485.
2. Liu SR, Zuo QH. Neonatal screening for phenylketonuria. Chin J Pediatr 1985;23:321-4.
3. Chen RG, Qian DL, Guo H, et al. Clinical results of PKU patients treated with local-made low-phenylalanine diet (Pantonin). Chin J Pediatr 1990;28:258-60.
4. Chen RG, Qian DL, Pan XS, et al. Persistent hyperphenylalaninemia: report of 5 cases. Chin J Pediatr 1988;26:18-20.
5. Chen RG, Qian DL, Pan XS, Zhang YF, Guo H, Gu XF. Malignant PKU: three cases of biopterin synthetase deficiency. Natl Med J China 1989;69:179-80.
6. Song F, Wu GY, Xu GZ, Chai WN, Ding XY. Frequencies of five point mutations of phenylalanine hydroxylase and prenatal gene diagnosis of phenylketonuria. Chin J Med Genet 1995;12:321-4.
7. Gu XF, Zhang M, Chen RG. Phenylketonuria mutations in southern Chinese: detected by denaturing gradient gel electrophoresis in exon 7 of PAH gene. J Inherit Metab Dis 1995;18:753-4.
8. Yuan LF, Huang SZ, Lo HY, et al. Prenatal diagnosis of classical phenylketonuria in 16 pregnancies with high risk. Chin J Med Genet 1995;12:327-9.