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ATYPICAL PHENYLKETONURIA CAUSED BY TETRAHYDROBIOPTERIN SYNTHESIS DEFICIENCY: NEONATAL SCREENING, DIAGNOSIS, HETEROZYGOTE DETECTION AND PRENATAL DIAGNOSIS

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The incidence of "atypical" phenylketonuria (PKU) due to tetrahydrobiopterin (BH_4) deficiencies among Caucasian hyperphenylalaninemics is estimated to be 1.5-2%.[4] The BH_4 deficiencies may be caused by deficient activity of GTP cyclohydrolase I, dihydropteridine reductase, or "dihydrobiopterin synthetas" (DHBS). Very few cases of atypical PKU in Chinese as well as people of other Oriental origins has been reported.

A method of urinary pterins analysis by reverse phase high performance liquid chromatography (HPLC) for differential diagnosis and detection of neterozygotes of atypical PKU has been established in our laboratory. Three PKU's were detected by screening blood Phe of 4,744 mentally retarded school children in Taiwan, and one of them with mild mental retardation (IQ 70, age 15Y) was caused by DHBS deficiency. From our neonatal screening program (1984.1-1986.6), the only PKU case found from 39,612 neonates by screening of blood Phe was caused by DHBS deficiency. BH_4 replacement therapy and treatment with neurotransmitters were started at age of 37 days and 9 months, respectively. Mild developement delay (DQ 78) was observed during last follow up (age:1Y9M). Another case of PKU detected by National Taiwan University Hospital from screening of 22,540 neonates (1981.9-1983.11) was diagnosed by us as a mild form of DHBS deficiency at age of 3.5 years old. Of the other 11 PKU diagnosed by our laboratory through pediatric clinics and family studies, 6 were atypical and were caused by DHBS deficiency. Four of the atypical PKU's expressed very severe neurologial symptoms. 11 out of 22 members of 2 atypical PKU families were found to be heterozygotes (50%). Analysis of pterins in amniotic fluid by another modified HPLC method enabled us to perform prenatal diagnosis for the preganancy at risk of DHBS deficiency. A case of heterozygote was born after the correct prenatal diagnosis.

Since we started our PKU research in 1982, 17 Chinese PKU cases have been diagnosed by us in Taiwan. Nine of them (53%) were atypical PKU and all the atypical PKU were caused by DHBS deficiency. These results indicate that the atypical PKU in Chinese is not an "atypical" form. Differential diagnosis of variant forms of PKU should be carried out for all the high Phe cases detected by neonatal screening, especially in Chinese, to select an appropriate therapy.