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■ Case report ■

A case of two sisters births from mother with phenylketonuria lacking mental retardation

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= Abstract =

In this untreated classic phenylketonuria (PKU) case, mental retardation is severe; however, there have been individuals- like the mother of this case- who have escaped mental retardation and all the other potential sequelae of phenylketonuria, despite having high blood phenylalanine levels, and very poor dietary control. It appears that they have nearly normal brain phenylalanine levels despite high blood phenylalanine (Phe) levels. A number of studies have now demonstrated considerable variability in blood vs. brain phenylalanine levels in phenylketonuria patients. Outcome of phenylketonuria appears to be related to brain phenylalanine levels. We report a case of "undiagnosed" maternal phenylketonuria syndrome. A female infant had low birth weight (2,400 g) with microcephaly. We examined her family and discovered that her mother was an undiagnosed phenylketonuria patient with a borderline intelligence quotient (IQ). The infant's sister, six years old, was diagnosed with phenylketonuria at the age of four years was mentally retarded and had received an operation for cleft lip and palate. the sister had also had a low birth weight (2,300 g). Her sister and mother were compound heterozygotes (mother: R243Q/Y325X; sister: Y325X/P407S). The infant and father were heterozygous carriers (baby: R243Q/－; father: P407S/－). **(Korean J Pediatr 2008;51:546-550)**

Key Words : Phenylalanine, Phenylalanine hydroxylase, Phenylketonuria, Maternal phenylketonuria syndrome

Introduction

Children with classic phe nylketonuria have an intelligence quotient (IQ) below 50 and seizures are common in the more severely retarded[1]. However, there have been individuals with so called “severe” phenylketonuria who have escaped retardation and all the other potential sequelae of phenylketonuria despite high blood phenylalanine levels and very poor dietary control[2-5].

Increased phenylalanine of these female individual during pregnancy can cross the placenta and affect specific fetal organs during development. The presence and severity of the fetal anomalies directly correlate with the maternal phenylalanine level. These fetal anomalies include microcephaly, dysmorphic facial features, esophageal atresia, congenital heart defects, intrauterine growth retardation, developmental delay, and impaired cognitive development[1].

We report a case of a female infant exposed to maternal phenylketonuria, Her older sister was diagnosed with phenylketonuria at 4 years of age. The mother, however, didn't know that she had phenylketonuria because she had borderline IQ.

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Case report

A female baby was born after full-term pregnancy with low birth weight (2,400 g, below 10 percentile), 45 cm of height (10 percentile) and 30 cm of head circumference (below 3 percentile). On physical examination, no other specific anomalies were found except for microcephaly. Her blood pressure, pulse, respiratory rate and body temperature were 84/46, 147/min, 50/min, 36.7℃, respectively. Laboratory test results were shown as follows: hemoglobin, 15.9 g/dL; hematocrit, 46%; white blood cell count, 21,600/mm^3; platelet, 387,000/mm^3. The levels of Na, K, AST, ALT, BUN, and creatinine were all within a normal range. IgM specific for Toxoplasma, Rubella, Cytomegalovirus, and Herpes simplex

virus was all negative. The karyotype was 46 XX normal chromosome. Phenylalanine was within a normal range (2 mg/dL at neonatal screening test, and 1.2 mg/dL at blood) and no prominent abnormality was found at urine amino acid and organic acid analyses. As she displayed perioral cyanosis during feeding, we checked esophagogram and then found gastroesophageal reflux. Her chest X-ray and brain ultrasonogram were normal. At echocardiogram, we could not discover other anomalies except for a small-sized ostium secondum atrial septal defect.

At follow-up after 2 years and 5 months, her weight was 11.2 kg (10 percentile). Her height was 85 cm (25 percentile) and head circumference was 42.5 cm (below 3 percentile). Her language development was significantly delayed. Mental development index (MDI) was below 50, and psychomotor development index (PDI) was 56 at BSID II (Bayley scales of infant development II test).

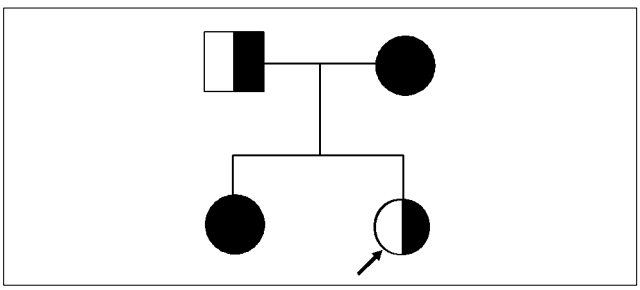

Fig. 1. Pedigree of the family with PKU. Mutations in the PAH gene identified in each family member are indicated.

Family history (Fig. 1)

Older sister : She was diagnosed as phenylketonuria at the age of 4 years old at another hospital. She was born after full-term pregnancy with low birth weight (2,400 g). She had undergone a surgical operation because of cleft lip and palate. At this time, she was 6 years old, her weight was 15 kg (3 percentile), height was 100 cm (below 3 percentile), head circumference was 45 cm (below 3 percentile). She also had moderate mental retardation (IQ<50) with attention deficit hyperactive disorder.

Mother : Mother delivered the second baby of this case at 30 years of age, not knowing that she had phenylketonuria. Her height was 153.2 cm, weight was 60 kg. She has light brown hair. Although the sign of musty odor was uncertain, she had an unpleasant smell when talking together. Her IQ was 77 (Verbal IQ : 80, Performance IQ : 77, total IQ : 77) at Korean Wechsler Intelligence scale. She graduated from highschool. The level of her blood Phe was 25.5 mg/dL. The level of urine-phenylacetic acid (387 mmol/mol cr, reference range : 0-2), 2-hydroxyphenylacetic acid (2,181 mmol/mol cr, reference range : 0-4), phenylpyrubic acid (7,878 mmol/mol cr, reference range : 0) were markedly elevated.

Mutation analysis : After obtaining informed consent, blood samples were collected from the patient and her family members. Genomic DNA was isolated from peripheral blood leukocytes using a Wizard genomic DNA purification

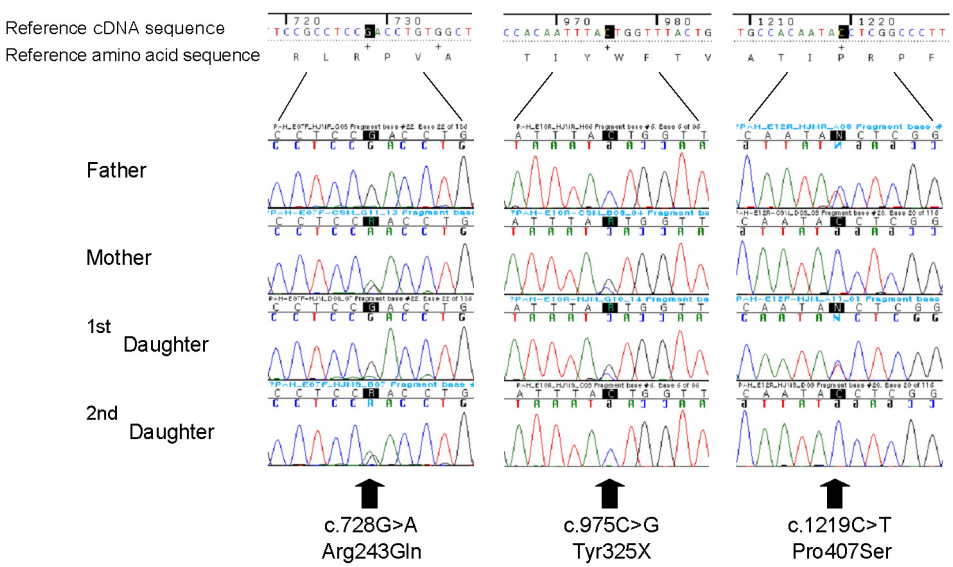

Fig. 2. Direct sequencing of phenylalanine hydroxylase (PAH) gene revealed that the sister and mother were compound heterozygotes (mother : R243Q/Y325X1 sister : Y325X/P407S). The infant and father were heterozygous carriers (baby: R243Q/-; father: P407S/-).

kit following the manufacturer's instructions (Promega, Madison, WI, USA). All 13 coding exons of the phenylalanine hydroxylase gene were amplified by polymerase chain reaction (PCR) using the primers designed by the authors. Cycle sequencing was performed with a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA) on the ABI 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). Interestingly, the infant was a heterozygous carrier of R243Q mutation. Further analysis of her parents and an elder sister demonstrated that her mother was a compound heterozygtes with R243Q and Y325X mutations and her sister was also compound heterozygous for Y325X and P407S. The P407S mutation identified in the sister was found in her father, a heterozygous carrier (Fig. 2).

Discussion

Phenylketonuria is an autosomal recessive metabolic disorder caused by a deficiency of phenylalanine hydroxylase (PAH). Phenylalanine hydroxylase is normally found in liver, kidney and pancreas but not in brain or skin fibroblasts. Phenylalanine hydroxylase catalyzes hydroxylation of phenylalanine to tyrosine using tetrahydrobiopterin (BH4) as cofactor. The phenylalanine hydroxylase deficiency trait is heterogeneous with a continuum of metabolic phenotypes ranging from classical phenylketonuria to mild hyperphenylalaninemia. Elevated phenylalanine appears to be the cause of neurotoxicity. In the untreated classic phenylketonuria case, mental retardation is severe[1].

The PAH gene on chromosome 12 (12q22-q24) spans 90 kb and contains 13 exons. The mutation profile of the phenylalanine hydroxylase gene is not restricted to any one region but spreads throughout the entire structural domains and shows enormous diversity. Almost 500 mutations have been reported throughout all exons and flanking sequences. A detailed account of PAH mutant alleles and other DNA variations is maintained at the PAH mutation analysis consortium website[6]. The majority of these mutations result in deficient phenylalanine hydroxylase activity and cause hyperphenylalaninemia. Most DNA alterations are missense mutations, although splice, nonsense, frame shift mutations, large deletions, and insertions have been identified. Most patients are compound heterozygotes, carrying a different mutant allele on each chromosome. Prevalences of specific mutant alleles differ from population to population. Mutant alleles R408W, IVS12ntl, IVS10nt11 are severe mutations that account for about 50% of mutant alleles in Europeans, but rare in Asians. R243Q, R413P, and Y204C are common in Asians, but rare in Europeans[7]. In Korean phenylketonuria patients, the R243Q, IVS4-1G>A, and E6-96A>G were the most relevant mutations[8]. The mother of this case has also the R243Q mutant allele. Several studies have shown that PAH genotype is one of the main determinants in phenylketonuria severity. Characterization of phenylalanine hydroxylase mutations is helpful tool for phenotype prediction in a newborn and for refining diagnosis and implementing optimal dietary therapy[8-11].

However, phenylalanine hydroxylase genotype does not always correlate with phenotype[2, 9-10]. There have been individuals like the woman of this case with so called "severe" phenylketonuria mutations who have escaped mental retardation and all the other potential sequelae of phenylketonuria despite high blood Phe levels and very poor dietary control[2-5]. Even in the siblings with the same phenylalanine hydroxylase genotype (R408W/R111X), a striking difference in intellectual function exists. The older sibling was diagnosed with phenylketonuria at the age of 4 years and given treatment. His IQ was 97 at 26 years of age. The younger brother was diagnosed with phenylketonuria at the age of 11 months and given treatment. His IQ was below 25 at 22 years of age[12]. It appears that the reason why they have escaped the usual consequences of dietary indiscretions is that they have near normal brain phenylalanine levels despite high blood phenylalanine levels. A number of studies have now demonstrated considerable variability in blood vs. brain phenylalanine 1eve1s in phenylketonuria patients. Outcome in phenylketonuria appears to be related to the brain phenylalanine levels[3-5]. Various environmental factors and modifying genes, such as the blood-brain barrier phenylalanine transporters, and variations in brain phenylalanine consumption rate may affect intellectual function in phenylketonuria patients[5, 13-15].

The pathogenesis of mental retardation in phenylketonuria is not completely understood. Defective brain myelination may be related to decreased biosynthesis of myelin proteins, because brain protein synthesis is inhibited by excessive phenylalanine[16]. Central nervous system effects may be ascribable to more global amino acid imbalances; elevated phenylalanine may affect the central nervous system concentrations of neutral amino acids by competitive inhibition of a shared amino acid transporter with relative

brain deprivation of tyrosine, tryptophan, and branched-chain amino acids[17]. Phenylalanine is a competitive inhibitor of both tyrosine and tryptophan hydroxylases, which are key enzymes in the biosynthesis of the neurotransmitters, dopamine and serotonin. Depletion of catecholamines and serotonin occurs in untreated patients with phenylalanine hydroxylase deficiency. Alterations within the brain in phenylketonuria are nonspecific and diffuse. They involve gray and white matter; and they probably progress with age. The types of alterations are interference with the normal maturation of the brain[18], defective myelination, and diminished or absent pigmentation of the substantia nigra and locus ceruleus[19].

Elevated maternal blood phenylalanine can cross the placenta and cause fetal birth defects, including microcephaly, dysmorphic facial features, esophageal atresia, congenital heart defects, intrauterine growth retardation, developmental delay, and impaired cognitive development[1]. MRI in these children showed hypoplasia or partial agenesis of the corpus callosum and delayed myelination[20].

The mother of this case didn't know that she had phenylketonuria. However, it is likely that mother's elevated blood phenylalanine might cross the placenta, and cause fetal birth defects. The sisters of this case showed microcephaly, intrauterine growth retardation, developmental delay, and impaired cognitive development.

This disease has been found in all parts of the world, and is the most common inborn error of metabolism in the white population, with an average incidence of 1 in 10,000, in Caucasian[7], and 1 in 41,000 in Korea[8]. Because there have been individuals like this case, to check the family history is desirable.

한 글 요 약

정신 지체가 아닌 페닐케톤뇨증 산모에서 출생한 자매 1례

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전형적 페닐케톤뇨증에서 식이 요법을 조기에 실시하지 않으면 생후 1세경에는 지능 지수가 50이하로 심한 정신지체가 된다고 알려져 있으나, 일부에서는 심한 정신 지체를 보이지 않기도 한다. 그 기전은 확실치 않으나 혈장에서보다는 뇌에서의 페닐알라닌 수치와 관련이 있을 것으로 생각되고 있다. 또한 페닐케톤뇨증 여성이 임신을 한 후 식이조절에 실패하게 되면 증가된 혈중 페닐알라닌이 태아에 영향을 주어 출생 후 저체중, 소두증, 선천성 심질환, 발달 지연, 지능 저하, 등이 올 수 있다. 따라서 전체 임신 기간 중 산모의 혈장 내 페닐알라닌을 6 mg/dL 미만으로 유지하도록 조절하여야 한다. 본 증례의 산모는 정신 지체는 아니었으므로, 본인이 페닐케톤뇨증 환자인지 모르고 지내다가 두 자녀를 출산하였다. 첫째아이는 4세경에 타병원에서 페닐케톤뇨증으로 진단받았으며, 저출생체중과 구개열의 수술병력 및 소두증이 있었다. 둘째아이는 페닐케톤뇨증은 아니었으나, 저출생체중과 소두증, 및 발달 지연을 보이고 있다. PAH유전자 분석에서 환아의 어머니는 R243Q/Y325X, 환아의 언니는 Y325X/P407S로 compound heterozygotes 임을 확인하였다. 환아의 아버지와 환아는 각각 P407S/- 및 R243Q/-를 가진 heterozygous 보인자이었다. 따라서 페닐케톤뇨증 환자 중 일부에서는 심한 정신 지체는 없이 일상적인 생활을 하는 경우도 있으므로, 출생아에서 원인이 밝혀지지 않는 저체중, 소두증, 지능 발달 지연 등이 있을 때는 가족력을 확인해 볼 필요가 있다.

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