P37

UNUSUAL PRESENTATION OF MILD HYPERPHENYLALANINEMIA IN A PRETERM INFANT ?

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Neonatal screening performed on the fifth day of life of a white caucasian girl (third child of nonconsanguinous parents) revealed a high phenylalanine value (23 mg/dl) indicative of classical phenylketonuria. However, on recall, phenylalanine determination on the ninth and tenth day of life gave normal values (2.6 and 0.5 mg/dl, respectively). Apart from a low tyrosine and a moderately decreased threonine amino acid analysis of plasma was normal.
The child was born by caesarean section in the 27 week of pregnancy because of intrauterine developmental delay and calcifications in the placenta. Postnatal course was uneventful except for a sepsis like episode the third day of life. Antibiotic treatment was initiated. However, no infectious agent could be identified and the condition resolved spontaneously. Protein intake after birth did never exceed the amount adequate for age and weight. The further follow up revealed moderately elevated plasma concentrations of phenylalanine (maximum 7 mg/dl) suggesting the diagnosis of mild hyperphenylalaninemia. Actually the patient is doing well without dietary therapy.
We tried to rule out possible reasons for these initially discrepant phenylalanine values. A false positive finding in the neonatal screening due to interference in the fluorimetric assay e.g. by antibiotics was excluded by reinvestigating the original guthrie card by ion exchange chromatography that confirmed the screening result. Again, there was no tyrosine elevation in this sample. A possible sample mix up was ruled out by a genetic fingerprint analysis on the original guthrie card clearly demonstrating the identity of the patient. Atypical phenylketonuria due to a defect in biopterin biosynthesis was also excluded by a biopterin load. Parental nutrition was given only initially and at a low dosage thus not being a plausible cause for the elevated phenylalanine value. Prematurity with impairment of liver function is known to be a possible cause of elevated aromatic amino acids or generalised hyperaminoacidemia. However, this was not found in our patient and the phenylalanine hydroxylation pathway is usually considered to be mature even in extreme premature newborns.
Thus, no obvious explanation for the neonatal screening result could be identified. We hypothesise that this course might represent an unusual onset of hyperphenylalaninemia in a preterm newborn. Moreover, this case underscores again that discrepant results in newborn screening need careful reevaluation and follow up in order to avoid screening failures.

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P38

MUTATION CHARACTERIZATION OF CHINESE PHENYLKETONURIA CAUSED BY 6-PYRUVOYL-TETRAHYDROPTERIN SYNTHASE DEFICIENCY

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Deficiency in 6-pyruvoyl-tetrahydropterin synthase (PTPS) activity is a major cause of the tetrahydrobiopterin (BH_4) deficient phenylketonuria. In this study, seven single base mutations at nucleotides 73 (C>G), 155 (A>G), 166 (G>A), 209 (T>A), 259 (C>T), 286 (G>A), and 317(C>T) as well as two nucleotide deletions 116-119del and 164-165del in PTPS gene were detected in Chinese PTPS deficient PKU by polymerase chain reaction and solid phase DNA sequencing. These nucleotide alterations and deletions resulted in Arg25Gly, Asn52Ser, Val56Met, Val70Asp, Pro87Ser, Asp96Asn, and Thr106Met amino acid substitutions and Lys38X and Lys54X frameshift stop, respectively. By analysis of 42 unrelated Chinese PTPS mutant alleles, the allele frequency of these mutations in Chinese PTPS deficient PKU were determined to be around 4.8% (73C>G), 35.7% (155A>G), 7.1% (166G>A), 2.4% (209T>A), 33.3% (259C>T), 7.1% (286G>A), 2.4% (317C>T), and 4.8% (deletions), respectively. However, none of 100 normal alleles screened were found to have these nucleotides changes. The 155A>G and 259C>T mutations were found to be account for 69% of the Chinese PTPS mutant alleles. The 155A>G mutation accounts for 52% of the southern Chinese PTPS mutation, but only one (9%) of the northern Chinese PTPS mutant allele was found to be 155A>G. The results indicated that 155A>G and 259C>T transitions are common mutations in Chinese PTPS deficient patients and the 155A>G mutation might be a southern Chinese mutation. Clinically, the 166G>A mutation was found to associate with the mild form of PTPS-deficiency. On the other hand, the 73C>G, 155A>G, 259C>T, and 286G>A were found mainly in the patients with severe clinical symptom.