6-PYRUVOYL TETRAHYDROPTERIN SYNTHASE DEFICIENCY: A CASE REPORT

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Abstract. A 5 day old girl screened positive for hyperphenylalaninemia on routine newborn screening. Initial diagnostic work-up showed elevated blood phenylalanine of 1100 mmol/L and low tyrosine. Limited protein diet and phenylalanine-free formula were prescribed. Further investigation revealed a defect in biopterin metabolism. Urine had no detectable biopterin (BH4) and an elevated level of neopterin at 24.31 mmol/mole Cr. Enzymatic assay showed zero level of 6-pyruvoyl tetrahydropterin synthase. The activity in the mother was 3.5 or 19.9% of controls consistent with heterozygosity. The concentrations of 5-hydroxyindoleacetic acid and homovanillic acid in the cerebrospinal fluid were below the reference ranges. A treatment regimen of BH4 tablets, 5 hydroxytryptophan and DOPA was initiated. The diagnostic evaluation, management and follow-up of patients with this disorder will be outlined. This is the first reported case of a Filipino with a defect in biopterin metabolism.

CASE HISTORY

IT was born full term by spontaneous vaginal delivery to a 29-year-old Filipino Chinese. Apgar scores were 8 (1 minute) and 9 (5 minutes). She was small for gestational age with a birth weight of 2,134 g and a length of 45.0 cm. Antibiotics were given for suspected neonatal sepsis because she presented with poor suck, tachypnea, and hyperbilirubinemia. The septic work-up was negative. After a week, the symptoms resolved and IT was discharged well.

Newborn screening done on the 5th day of life revealed increased phenylalanine (phe) of 1,100 mmol/l. A modified diet was started consisting of phenyl-free formula simultaneous with limited breast milk feedings. IT was maintained on this diet until she left at one month of age for a full metabolic evaluation abroad.

On admission at the University of California San Diego Medical Center, she weighed 2.52 kg and measured 45 cm. Her head circumference was 37.3 cm. She was very jittery and irritable. Initial random blood sugar was 60 mg%. Plasma phe was very low at 9 mmol/l. A full protein challenge resulted in a markedly elevated phe level of 2,522 mmol/l after 24 hours. This suggested the diagnosis of classic phenylketonuria (PKU) for which the dietary regimen was commenced. Meanwhile, blood for phenylalanine hydroxylase (PAH) mutational analysis and urine for pteridine determination were sent.

During the course of the out patient clinic visits, plasma phe levels were monitored. These quickly decreased especially when the phenyl-free formula was increased. IT began to thrive but remained irritable and would arch her back. She would have vomiting episodes.

Table 1. Summary of diagnostic evaluations.

1. Mutational analysis of PAH		negative
2. CSF Metabolites		
	5-HIAA	low
	HVA	low
	Methyldopa	normal
	BH4	zero
	Neopterin	normal
3. Urine pteridines		
	Biopterin	zero
	Neopterin	high
4. DHPR activity		5.32% (normal)
5. 6 PTS activity		
	patient	zero
	mother of patient	19.9%
6. Baseline EEG and MRI, brain		normal

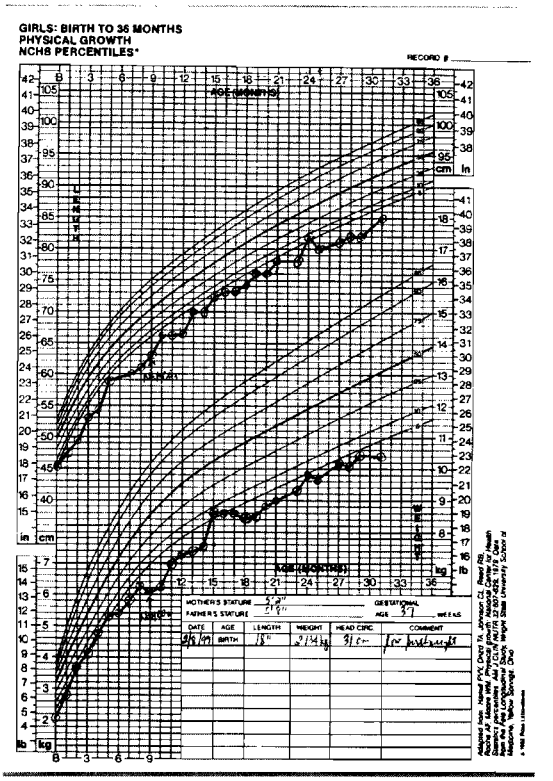
The PAH mutational analysis was negative. The urine pteridine showed zero biopterin and high neopterin. The activity of the DHPR enzyme was normal at 5.32%. The data suggested a defect in biopterin synthesis. The activity of the enzyme 6- pyruvoyl tetrahydrobiopetrin synthase was zero. Mom's level was 19.9 %.

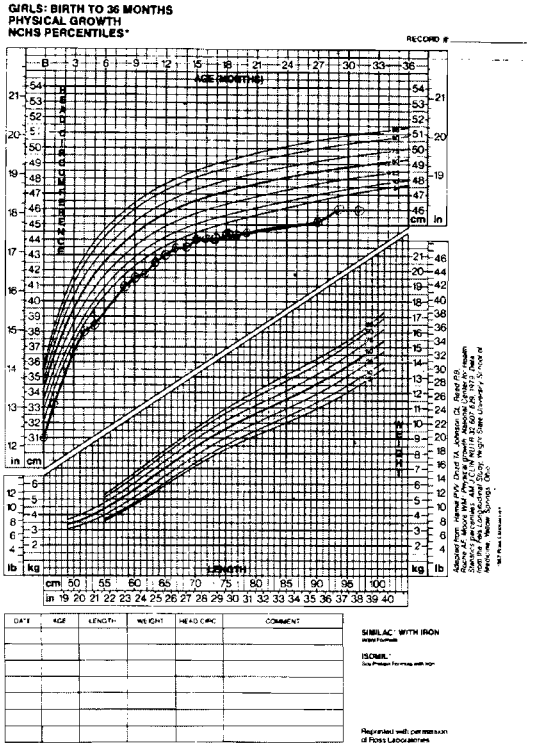
With these data, the treatment regimen was revised to include biopterin, DOPA and 5 hydroxytryptophan (5-HT). Full protein feedings were re-introduced. IT begun to thrive and after a month, her weight increased to 4 kg.

Currently, IT shows a mental age that is appropriate for her chronological age of 36 months; but her speech is delayed (~14 months). She is currently undergoing speech and language therapy. Her growth is subnormal and her head circumference tends to be smaller that the rest of her anthropometric measurements. (see Figs 1 and 2).

DISCUSSION

Tetrahydrobiopterin (BH4) deficiencies are metabolic disorders affecting the biosynthesis of





catecholamines, serotonin and phenylalanine. Four disorders have been defined: GTP cyclohydrolase I (GTPCH); 6-pyruvoyltetrahydropterin synthase (6PTS); dihydropteridine reductase (DHPR) and 4α-carbinolamine dehydratase (PCD). Most present with elevated phenylalanine (phe) and account for 1-2% of hyperphenylalaninemia (HPA) detected on newborn screening. Inheritance is autosomal recessive.

Symptoms may manifest during the first weeks of life, but are usually noted at about four months of age. However, when information about the neonatal period is provided, a careful review indicates that abnormal signs (poor suck, decreased spontaneous movements, "floppy baby") can be noticed even during the neonatal period. Birth is generally uneventful, except that there is a higher incidence of prematurity. Lower birth weight is typical in (severe) 6PTS deficiency. Our patient, IT was small for gestational age.

The clinical course of the illness is similar in untreated patients with typical (severe) forms of GTPCH, 6PTS, and DHPR deficiencies. The variable but common

Table 2. Types of BH4 deficiencies

Enzyme	Gene locus	Mutations	Incidence (n = 420)
GTPCH	Chr 14	42 (non-HPA)	4%
6 PTS	Chr 11	28	59%
PCD	Chr 10	7	5%
DHPR	Chr 4	21	32%

symptoms are mental retardation, convulsions (grand mal or myoclonic attacks), disturbance of tone and posture, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infections, hypersalivation, and swallowing difficulties. Diurnal fluctuation of alertness and neurologic symptoms are also reported. There is limited data about microcephaly. In GCTPH-deficient patients where there were serial head measurements, progressive microcephaly was noted with increasing age, whether patients were treated or not.

The absence of clinical signs, theoretically, defines phenotypically atypical forms. However, in some infants with a 6PTS deficiency, neonatal hypotonia or acute but transient behavioral abnormalities, neurovegetative signs, and sleeping difficulties were noted. Our patient at some point had posturing and sleep problems. In two patients with a DHPR deficiency investigated there were no signs of neurological symptoms until two years of age. However, one patient later developed decelaration in head growth velocity, whereas psychomotor development continued to be normal for age. In patients with PCD deficiency, slight upper limb tremors after stimulation and a moderate tendency to hypertonia were noticed in one child, and transient hypotonia and motor delay in another. With control of blood phenylalanine levels, symptoms receded.

The goals of treatment include control of hyperphenylalaninemia, restoration of neurotransmitter deficiencies and insurance of best neurodevelopmental status. Medications include BH4, 5 hydroxytryptophan, DOPA/Carbidopa. Blood phenylalanine and tyrosine levels, CSF neurotransmitters and Prolactin (alternative to CSF neurotransmitters) should be monitored.

In any patient who presents with hyperphenylalaninemia, diagnostic evaluation for BH4 metabolism must be done. The dietary management of a patient with a deficit in BH4 metabolism requires no protein restriction provided BH4 tablets are given.

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