

Danger of high-protein dietary supplements to persons with hyperphenylalaninaemia

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Summary: A 16-year-old adolescent with mild hyperphenylalaninaemia was given a high-protein 'body building' supplement twice daily, causing headaches, decreased school performance and mild depression. All symptoms disappeared after cessation of the supplement. The phenylalanine hydroxylase mutation H170D/IVS1nt5G>T was found to be responsive to tetrahydrobiopterin with significant decrease in blood phenylalanine concentration and increase in tyrosine blood content. A brain phenylalanine level of 0.5 mmol/L was initially documented, which decreased to the normal carrier range of 0.2 mmol/L within one month of discontinuance of the protein supplement. At present, the patient is on a normal diet without phenylalanine restriction.

Persons with mild forms of hyperphenylalaninaemia (HPA), consistent with blood phenylalanine (Phe) concentrations of 120–600 µmol/L (Levy et al 1971), often consider themselves to be perfectly normal because they do not require a Phe-restricted diet (Weglage et al 2001). Many are lost to follow-up (Lang et al 1989; Smith et al 2000) even when identified by newborn screening as prime suspects for a diagnosis of phenylketonuria (PKU; McKusick 261600). In fact, an unknown number probably escape detection by the present standards of newborn screening programmes utilizing 240 µmol/L as a cut-off for referral to a clinical resource for evaluation of their mild degree of HPA (Bonafe et al 2001). Normal individuals exhibit blood Phe concentrations of 45–90 µmol/L; carriers of one PKU gene are thought to exhibit blood Phe concentrations of 100–200 µmol/L (Bickel 1970). Persons with blood Phe concentrations of 120–600 µmol/L classified as having HPA are usually

not treated unless they are female, when slightly elevated levels of blood phenylalanine might become dangerous during pregnancy (Levy et al 1994). Recently two persons with mild HPA with complications and blood Phe concentrations usually below 600 $\mu\text{mol/L}$ have come to our attention. The first has already been reported (Koch et al 2002). The second is the subject of this report.

CASE REPORT

This Hispanic boy was born by Caesarian section after a normal pregnancy. His measurements were in the normal range according to standards. The mother was a 29-year-old gravida 3 para woman and there was no history of HPA or mental retardation on either side of this family. He was breast-fed until 9 days of age, when he was referred to the Children's Hospital of Los Angeles because of two positive newborn screening Phe values of 360 and 720 $\mu\text{mol/L}$ on the 3rd and 6th days of life, respectively. While hospitalized he was started on a Phe-restricted diet and a diagnosis of mild PKU was suggested. He received a combination of breast milk and a Phe-restricted medical product until 1 year of age. His blood Phe control was excellent, with levels usually in the range 240–480 $\mu\text{mol/L}$. He continued the consumption of the Phe-free medical product until age 13 years, when it was discontinued due to his normal protein intake and blood Phe concentrations remaining in the range 300–444 $\mu\text{mol/L}$. Tyrosine levels also remained within normal ranges.

At 15 years of age, he participated in sports and his coach suggested that he consume a 'body building' high-protein product (Just-WHEY, SportPharma, Concord, CA, USA) containing 16.25 g essential amino acids and 45.5 g nonessential amino acids per 100 g (Table 1). He was advised to take 30 g twice a day mixed with water. Within a month, he began to experience headaches requiring over-the-counter preparations, such as paracetamol (acetaminophen). Subsequently the headaches became more severe and required an emergency room visit. He returned to Children's Hospital for a follow-up evaluation because

Table 1 Amino acid profile per 100 g of the product Just-WHEY

<i>Essential amino acid</i>	<i>g/100 g</i>	<i>Nonessential amino acids</i>	<i>g/100 g</i>
L-Leucine	8.59	L-Alanine	4.4
L-Isoleucine	5.39	L-Arginine	2.1
L-Valine	4.7	L-Aspartic acid	8.7
L-Lysine	7.7	L-Glutamic acid	14.3
L-Threonine	5.9	L-Glycine	1.5
L-Methionine	1.7	L-Histidine	1.5
L-Phenylalanine	2.7	L-proline	6.2
		L-Serine	4.3
		L-Tyrosine	2.5
Total	16.25	Total	45.5

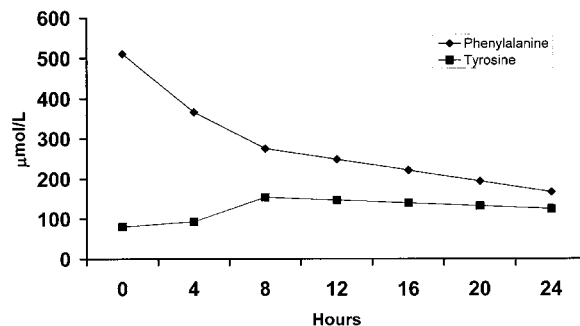


Figure 1 Blood phenylalanine and tyrosine response to a 10 mg/kg dose of tetrahydrobiopterin given at time 0

his grades in school had fallen and he appeared to his parents to be depressed. He was alert but complained of headaches. The physical and neurological examinations were normal. His height and weight remained at the 75th centile. Psychological evaluation revealed an IQ of 105 without verbal and performance discrepancy.

He had continued to ingest 30 g of the protein supplement twice daily. Nutritional assessment documented a protein intake of 1.43 g/kg per day, containing 4.32 g of phenylalanine and 3.72 g of tyrosine. His blood, urine and metabolic panel were normal. The plasma Phe concentration was 391 µmol/L and tyrosine was 56 µmol/L. Blood was also obtained for a determination of the Phe hydroxylase (PAH) mutation and dihydropteridine reductase activity and urine for tetrahydrobiopterin status. Magnetic resonance spectroscopy (MRS) revealed an increased brain concentration of 0.5 mmol/L compared to a simultaneous blood Phe concentration of 510 µmol/L.

We obtained an informed consent in accordance with the Children's Hospital Los Angeles internal review board requirements for a tetrahydrobiopterin (BH₄) load of 10 mg/kg. This produced a significant decrease in blood Phe from 510 µmol/L to 168 µmol/L within 24 h and an increase in tyrosine from 80 µmol/L to 125 µmol/L during the same period (Figure 1).

DISCUSSION

The response to the BH₄ challenge was anticipated after the identity of the boy's PAH mutations as H170D/IVS1nt5G>T (Guldberg and Guttler 1994; Kure et al 1999; Spaapen et al 2001; Trefz et al 2001); however, the elevation of brain Phe to 0.5 mmol/L was unexpected. At blood Phe concentrations of 360–480 µmol/L, the brain Phe level is usually within the carrier level of 0.1–0.2 mmol/L (Koch et al 2000; Moats et al 2000). After discontinuation of the protein 'body building' supplement, his headaches gradually abated and his school performance returned to normal. Follow-up evaluation over a period of several months demonstrated that

his clinical course had returned to normal and his brain Phe was reduced to 0.2 mmol/L.

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