HYPERPHENYLALANINEMIA IN THE PHILIPPINES

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Abstract. To present patients with hyperphenylalaninemia (HPA) diagnosed by routine newborn screening and to discuss the principles in managing hyperphenylalaninemia, retrospective clinical chart review was conducted. Newborn screening for phenylketonuria (PKU) was performed using the Guthrie Test or Bacterial Inhibition Assay, utilizing dried blood spots on special filter cards. Positive screens were confirmed through plasma amino acid determination, urinary pterins for tetrahydrobiopterin deficiency, enzyme analysis. Once confirmed, the patients were kept on low-phenylalanine diet and regularly monitored for blood phenylalanine levels and developmental profile. A total of 189,720 newborns were screened from 1996-2001. Seventy five screened positive for PKU; 41 returned for retest; 3 were confirmed positive for HPA. This paper presents the first two cases of HPA detected by the Philippine Newborn Screening Program. The management of each case upon diagnosis is discussed. The significance of early detection and treatment of HPA is emphasized.

INTRODUCTION

Hyperphenylalaninemia (HPA) is a spectrum of manifestations reflecting the degree of elevation of plasma phenylalanine. It results from a deficiency of phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine, causing a block in the hydroxylation pathway. Phenylalanine (phe) accumulates in the blood, leading to impaired mental development in untreated affected individuals.

The most severe of these is classical phenylketonuria (PKU), which presents with plasma phe concentrations above 1,000 μmol/l in the untreated state and a dietary phe tolerance below 500 mg/day (Clark, 1996). Non-PKU hyperphenylalaninemia (non-PKU HPA), on the other hand, presents with plasma phe concentrations consistently above normal (>120 μmol/l) but below 1,000 μmol/l on a normal diet. The other form of HPA, called variant PKU, is used for individuals who do not fit the description for either PKU or non-PKU HPA (Kayaalp *et al,* 1997).

The overall prevalence of PKU in Caucasian and Oriental populations is anywhere between 1 in 10,000-1:25,000 live births (Scriver *et al*, 2001). However, there is considerable variation in the prevalence rates of different ethnic groups. The Irish population has 1 in 4,500 prevalence (DiLella *et al*, 1986), for the Turks, 1 in 2,600, which reflects a much higher prevalence rate than what is seen globally. Still, other populations have lower prevalence rates, like the Japanese with 1 in 143,000 and the Ashkenazi Jews with 1 in 200,000 (Ozalp *et al*, 1986). In the Philippines, the prevalence of HPA is at 1 in 47,430. So far, only 3 cases have been detected through newborn screening (Project Update: Philippine Newborn Screening Project, 2001).

MATERIALS AND METHODS

Blood samples are obtained by heelprick and blotted onto (S & S 903) filter paper from infants after the first 24 hours of life. Dried blood spots were tested for elevated phe levels using the Guthrie Test/Bacterial Inhibition Assay. If the test yields a positive result (phe >200 μmol/l), the patient is recalled for confirmatory testing. A diagnosis of PKU is given when plasma phe is elevated, plasma tyrosine (tyr) is low and urinary pterins are normal.

Once the diagnosis of HPA or PKU is established, dietary protein restriction is initiated by keeping the patient on a phenylalanine-free formula and limiting the dietary intake of natural protein to 1 g/kg/day. Protein intake is later adjusted based on the patient's plasma phe levels. Regular monitoring of the patient's blood phe level is done, as well as regular neurodevelopmental assessments.

In this report, case histories of 2 patients with HPA detected by newborn screening are reviewed. These patients were recalled for an evaluation of their overall

physical condition and assessed neurodevelopmentally using the Denver II Developmental Screening Test. Blood for plasma phe and tyr levels was extracted and analyzed.

RESULTS

Case 1

HD was born full term by spontaneous vaginal delivery after an uncomplicated pregnancy to a 26 year-old primigravid, with a birth weight of 2,700 g. The parents were not related. Newborn screening done on the second day of life revealed elevated phe of 300 μmol/l (normal < 200 μmol/l). At three months, the blood phe level was 310 μmol/l.

Determination of dihydropteridine reductase (DHPR) activity showed a normal level at 1.9 μmol/min/disc (normal: 1-9 μmol/min/disc). Urine catecholamines and pterins were normal. Patient was then diagnosed to have Phenylketonuria with a mild deficiency of phenylalanine hydroxylase.

A biweekly monitoring of phe levels revealed mildly elevated values except for four episodes of blood phe levels reaching values slightly greater than 350 μmol/l. At age 11 months, the patient was assessed to be developmentally at par with his peers. No dietary modifications were done at this point.

At 1 year and 4 months of age, the blood phe level was noted to be 490 μmol/l and HD showed signs of developmental delay. Dietary modification was started. At 1 year and 5 months of age, the patient was re-evaluated and assessed to have an expressive language delay. The patient was scheduled for Brainstem Auditory Evoked Response (BAER) testing and speech evaluation.

Case 2

JI was born full term after an uneventful pregnancy with a birth weight of 3,600 g. The parents were not related. Newborn screening done on the second day of life revealed an elevated phe level of 370 mmol/l. Phe level at one month of age was 1,020 mmol/l. Low phenylalanine diet was started. Subsequent determinations of blood phe levels showed a gradual decline to 10 mmol/l by the third month of life. Development was at par with age. Patient was given a diagnosis of atypical PKU.

At 3 months, protein was increased to 2 g/kg/day with monthly monitoring of phe levels. At 5 months of age, phe levels were at 550 mmol/l and developmental assessment showed gross motor delay. Dietary protein was restricted to 1.6 g/kg/day and PKU milk was resumed. Subsequent phe levels ranged from normal to 1,020 mmol/l. Non-compliance and poor follow-up were the major concerns. Developmental assessment at 22 months of age revealed functional level of 12-15 months.

DISCUSSION

Hyperphenylalaninemias are inherited in an autosomal recessive manner. The gene responsible for the production and consequent activity of phenylalanine hydroxylase is the PAH gene which has been mapped to chromosome 12, in the region q22-q24 (Ryan *et al*, 1999). Mutations in this gene give rise to deficient PAH enzyme activity, which in turn causes the clinical phenotypes PKU, non-PKU HPA and variant PKU (Scriver *et al*, 2001).

Classic PKU puts the patient at a very high risk of developing profound and irreversible mental retardation if left untreated. Individuals affected with non-PKU HPA have a lower risk. The risk results from the excessive phe, which is toxic to the developing brain. Individuals with HPA or PKU also show a decrease in the amino acids tyrosine and tryptophan, the precursors of the neurotransmitters dopamine, norepinephrine and serotonin. Decreased myelin production is also evident. Later in life, these patients may exhibit exaggerated deep tendon reflexes and even paraplegia or hemiplegia. Other signs and symptoms of HPA or PKU include epilepsy and behavior problems (Pietz *et al*, 1998).

While classical PKU requires dietary phe restriction, there are no strict dietary recommendations for hyperphenylalaninemia. We have found it necessary to impose a limited phe intake for our patients in as much as they manifested with developmental delays even with only mild elevations of phe.

The diagnosis of HPA or PKU depends solely on laboratory examinations. Since persistent severe elevated blood phe levels will lead to impaired cognitive development that is irreversible, newborn screening of this disorder is of utmost significance.

CONCLUSION

This paper presents the first two cases of hyperphenylalaninemia detected by the Philippine Newborn Screening Program. The management of each case upon diagnosis was discussed. Althought the clinical course of these 2 patients are far from ideal, presenting their case summaries highlights the importance of vigilance

and regular monitoring of patients who screen positive on newborn screening.

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