

Brief communication

Tetrahydrobiopterin and maternal PKU

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Abstract

A 29-year-old woman with PKU is presented, who was successfully treated with phenylalanine restriction as well as oral BH4 during this pregnancy, with a normal outcome. Her PAH mutation was R408W/F39L. Remarkably, the blood phenylalanine control was easily accomplished during this pregnancy. The lack of nausea and vomiting during the first trimester suggests that the occurrence of CHD in babies born to women with PKU may be reduced with BH4.

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Introduction

Kure et al. [1] reported that tetrahydrobiopterin (BH4) was therapeutic and effective in decreasing blood phenylalanine (Phe) in persons with mild hyperphenylalaninemia (HPA). As a result of their findings, Matalon et al. [2] subsequently published additional results in which a few persons thought to have mild to moderate PKU also responded to oral BH4 with decreasing blood Phe levels. In fact the studies by Matalon et al. identified several women with PKU whose blood Phe levels could have been treated with BH4 to achieve levels of 120–360 µmol/L, the range recommended for treatment for maternal PKU [3]. In addition, BH4 has been used for some 30 years as a test for BH4 defects in the pathway of production of BH4 in neonates with initial elevation of blood Phe levels identified during the newborn period [4].

To date, no significant toxicity has been associated with its use. For a variety of reasons it has not been utilized to treat pregnant women with PKU. The International Study of Maternal PKU, which lasted for some 20 years [5]

included 48 women with mild hyperphenylalaninemia, who gave birth to 58 newborns, however only eight of them were actually treated with a Phe restricted diet and none with BH4.

Levy et al. [6] recently reported that these offspring demonstrated a follow-up mean intelligence quotient of 102 and that the eight treated and untreated pregnancies were comparable. One child at eight years of age was discovered with congenital heart disease with an aortic valvular lesion. In addition, eight of the offspring did exhibit a birth head circumference of 32 cm, or slightly below, but otherwise the overall conclusion was that mild maternal Phe levels of no more than 600 µmol/L during pregnancy did not require dietary treatment of Phe. As yet the treatment of maternal PKU with BH4 has been unreported. The purpose of this manuscript is to report the use of BH4 in the pregnancy of a woman with the PKU mutation of R408W/F39L. Approval by The Federal Food and Drug Administration was requested and obtained.

Case report

CJ was born in 1973 and was identified neonatally with the biochemical findings suggestive of classical PKU. Her mother's pregnancy was normal, however a caesarean

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section was performed because the first born to this 28-year-old gravida 2 para 1 mother required one. The infant's birth weight was 3600 g, length 49.5 cm, and the head circumference was 33.7 cm. The physical examination was normal, however the first blood Phe sample on the third day of life was reported as positive. She was referred to the PKU program at the Children's Hospital of Los Angeles where her first blood Phe level was reported as greater than 1200 $\mu\text{mol/L}$ and she was accordingly started on a Phe restricted diet. She was easily controlled with her Phe level maintained between 120 and 600 $\mu\text{mol/L}$. She was readmitted to the hospital at one year of age for a challenge procedure to confirm her diagnosis. On an evaporated milk challenge, which provided 180 mg of Phe per day, her blood Phe rose progressively to over 1800 $\mu\text{mol/L}$ by the third day and it was assumed that a diagnosis of classical PKU was confirmed (Fig. 1). During the intervening years, CJ remained on diet and attended two PKU camps sponsored by the California State Health Department. Her blood Phe level was nicely controlled until she went to college. During these latter years, her blood Phe levels ranged between 900 and 1200 $\mu\text{mol/L}$, however she continued to take the recommended amount of her Phe restricted product twice daily. She graduated with a teaching credential and taught school for several years. She has remained on a Phe restricted product but her Phe levels have been above the recommended levels of 600–900 $\mu\text{mol/L}$. Therefore, mutation analysis of the phenylalanine hydroxylase gene was performed through the courtesy of Flemming Guttler, in Denmark. This revealed the R408W/F39L mutation. Her intelligence testing, utilizing the Stanford Binet, Wechsler Intelligence Scale for Children and the Wechsler Adult Intelligence Scale varied between 97 and 110. She was subsequently included in the BH4 trials [2].

Surprisingly, she demonstrated a significant decrease in her phenylalanine levels over the following 24 h after receiving a dose of 10 mg/kg (Fig. 2). As a result of this study, she decided to remain on BH4 therapy and she stopped the Phe restricted product she had been taking for many years.

At 29 years of age, she married a lieutenant in the US Navy and went to Italy in 2000 with her husband. Initially they decided to adopt, rather than to have their own child. It was at that time in 2002 when the Maternal PKU Col-

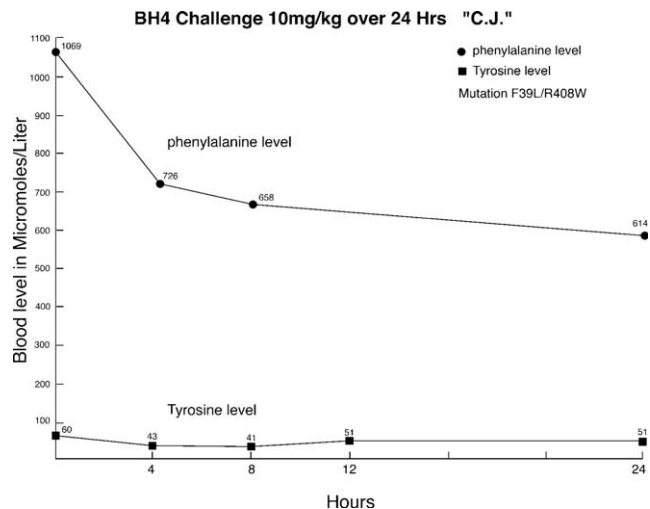


Fig. 2. Challenge with BH4 at 10 mg/kg per day and the response of phenylalanine decrease.

laborative Study published its report. There were three significant findings [4]. (1) Infants born to mothers who achieved recommended blood Phe control by eight weeks of pregnancy had similar intellectual development as those born to mothers who were in control at the time of conception, (2) poor protein and vitamin intake during the first trimester of pregnancy was associated with congenital heart disease in the newborns, and (3) blood Phe levels between 120 and 360 $\mu\text{mol/L}$ throughout the pregnancy were associated with a normal outcome. If the mother's IQ is less than 85 on a WAIS-R test, however, it is more difficult to keep the blood Phe levels in the recommended ranges [7].

With this knowledge, CJ and her husband decided to have their own baby. Two years prior to this time, she was ingesting 20 mg of BH4 twice a day on a normal diet. On this regime, her blood Phe levels ranged around 900 $\mu\text{mol/L}$. After conception, her BH4 therapy continued, but she ingested a Phe restricted product in addition. At the beginning of her second trimester, her BH4 was increased to 40 mg twice a day and she continued to ingest a Phe restricted product. At the beginning of the third trimester her BH4 was increased to 50 mg twice a day. The remarkable thing about her pregnancy was the

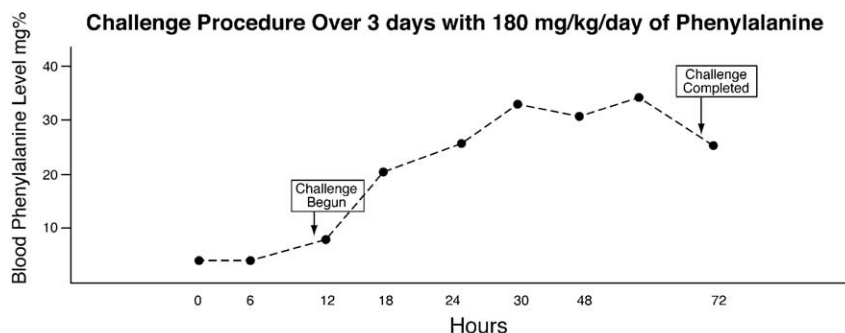


Fig. 1. Evaporated milk challenge with 180 mg of phenylalanine per kg per day for 3 days.

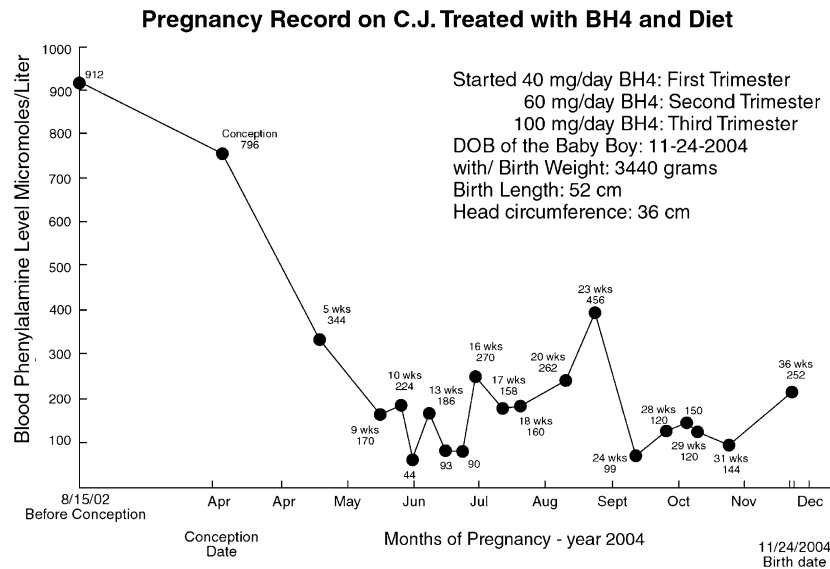


Fig. 3. Blood phenylalanine levels during pregnancy.

complete absence of any nausea or vomiting. Control was established with both restriction of phenylalanine during the pregnancy and with the ingestion of increasing amounts of BH4.

Fig. 3 details her blood Phe levels throughout the pregnancy on this regimen. Fetal ultrasound at this time was normal, and the baby's head and body were growing normally. The baby was born 2004, weighing 3440 g, measuring 52 cm in length with a head circumference of 36 cm. The fetal echo of the heart was normal.

Discussion

When the data from the Maternal PKU Collaborative Study was reported, it provided strong evidence that control of blood phenylalanine during pregnancy was compatible with a normal outcome. This was true even if the first 2 months of pregnancy were not within the recommended parameters of control. This conclusion was also supported by the data presented by Widaman and Azen [8].

In addition, pathological studies of normal neuronal development of the fetal brain show that it begins at 8–10 weeks of pregnancy. Thereafter, elevated blood phenylalanine in untreated pregnant women with PKU adversely affects intellectual development in the fetus. After eight weeks of pregnancy in women with untreated PKU, microcephaly is usually apparent in the infant at birth, as well as facial dysmorphism [9]. The normal outcome of this pregnancy supported the work of Imamura et al. [10] utilizing BH4 in pregnant guinea pigs. Imamura et al. showed that when BH4 was administered to a pregnant guinea pig, it passed through the placenta and stimulated phenylalanine hydroxylase production in the fetal liver. He suggested that BH4 administration should be part of the therapy for maternal PKU. If these observations are confirmed in a larger sample of pregnancies, it might be an exciting addition to our knowledge regarding the etiology of fetal mal-

development such as microcephaly [3] and congenital heart disease [11].

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