

BRIEF COMMUNICATION

Mental Illness in Mild PKU Responds to Biopterin¹

A 25-year-old woman with mild hyperphenylalaninemia developed disabling depression and panic attacks. The mutations on the phenylalanine hydroxylase gene indicated that she might be responsive to tetrahydrobiopterin therapy. Mutation analyses were performed by the John F. Kennedy Institute in Glostrup, Denmark. The response to tetrahydrobiopterin therapy was impressive at an oral dose of 50 mg twice a day. A 25-year-old woman with mild hyperphenylalaninemia due to a PAH mutation of IVS12nt1g→a/E390G has been treated for 1 year with BH₄ therapy. A maintenance dosage of only 100 mg/day has resulted in significant improvement of depression and panic attacks, with discontinuation of psychotropic medication. © 2002 Elsevier

Science (USA)

Key Words: phenylketonuria; tetrahydrobiopterin; mild hyperphenylalaninemia; mental illness.

The hyperphenylalaninemic categories are variable, but are categorized as classical, moderate, or mild phenylketonuria (PKU) and mild nonphenylketonuria (1). More unusual forms of hyperphenylalaninemia are due to defects in tetrahydrobiopterin (BH₄), the cofactor of phenylalanine hydroxylase (PAH) (2). Recently attention to the importance of the cofactor has been stimulated by the unusual finding that tetrahydrobiopterin itself (3,4) may play an important role in the treatment of persons thought to require dietary therapy with the phenylalanine (phe)-restricted diet (3). The discovery by Kure *et al.* (3) has been confirmed by other similar reports by Trefz *et al.* (6) and Spaapen *et al.* (7). At present it is known that responsiveness to BH₄ can be suspected in mutations of the PAH gene such as

E390G, Y414C, and A300S (8). This has resulted in an increased importance of identification of the various mutations in the PAH gene (9). The purpose of this report is to document the response to BH₄ in a 25-year-old woman with mild hyperphenylalaninemia affected by severe depression and recurrent panic attacks accompanied by decreased intellectual ability. Her panic attacks usually lasted only 1–2 min but occasionally 5–10 min. These mental disturbances interfered with her usual activities of meal preparation, care for her child, home cleanliness, and marital harmony.

PATIENT DESCRIPTION

This individual was referred as a newborn to the PKU program at the Childrens Hospital of Los Angeles from Nevada due to the finding of an elevated newborn screening test for PKU on a Guthrie test. The pregnancy had been healthy and the delivery was unremarkable. The mother was primiparous, was in good health, and denied smoking, ingestion of drugs, etc. The family history did not reveal any other persons who were mentally retarded or had PKU. The birth measurements revealed that the infant weighed 3400 g and measured 50 cm in length and the head measured 34 cm in circumference (all at the 50 percentile). The Guthrie blood phe level reported on the sixth day of life was greater than 1200 mmol/liter (normal <80–120).

While hospitalized the blood phe levels remained between 600 and 720 μ mol/liter on a normal infant formula (Similac) and a diagnosis of mild hyperphenylalaninemia was made. During the first year she progressed normally. At 1 year of age she scored a developmental quotient of 100 on a Gesell Scale. Blood phe levels on a free diet including solid foods remained at similar levels as previously documented while hospitalized. Since the family lived in another

¹ Supported by the Childrens Hospital Research Institute, Los Angeles, California, The Danish Medical Research Council, Copenhagen, Denmark, and The Swiss National Science Foundation Grant 31-54183.98.

state, the child was not seen again until 5 years of age at which time she presented with behavior problems and was having difficulty at school. She had also been classified as a slow learner. The physical examination was normal and an intelligence quotient was reported as 113 on a Stanford Binet test. Due to parental anxiety the child was started on a phenylalanine-restricted diet even though the blood phenylalanine levels were similar to those recorded earlier. All other studies including an electroencephalogram were reported as normal. Subsequently with good control of her blood phe levels between 120 and 360 $\mu\text{mol/liter}$ her behavior and school adjustment improved and at 10 years of age dietary treatment was discontinued. Another psychological assessment utilizing the Wechsler Intelligence Scale was reported as 95 at the time of dietary discontinuance. She was not seen again until age 25 years with her present illness. During the interim she married a man who was considerably older than herself and had a 1½ year old child (DQ 94). Her mental disturbances started at age 23 and she had been under psychiatric care receiving a variety of psychotropic medications for depression. Due to her failure to improve and the onset of panic attacks the parents again brought her to the PKU program and she was reevaluated. She was on sertraline 50 mg/day. This time she was grossly overweight at 150 kg and was 153 cm in height. The physical and neurological examinations were normal. Blood phe level was 630 $\mu\text{mol/liter}$ and her DNA analysis revealed IVS 12nt1g→a/E390G heteroallelic mutations. Kure *et al.* (2) had reported that the E390G mutation of the PAH gene was responsive to BH₄ therapy.

Since it was apparent that this individual was mentally depressed and this was having a deleterious effect upon her family it was decided to treat her with BH₄. A Wechsler Adult Intelligence Scale-Revised was reported as 83.

Inherited tetrahydrobiopterin deficiency was excluded by normal neopterin and biopterin levels in urine and plasma. Tetrahydrobiopterin tablets (50 mg) were purchased from Dr. Schircks Laboratories (Jona, Switzerland).

Initially the Food and Drug Administration in Washington D.C. was contacted and an Investigational New Drug permit was obtained since BH₄ still is not an approved drug for therapy. An informed consent was obtained. Dosage of BH₄ presented a problem. Finally it was decided to treat her with a small dose and increase it gradually over a period of time since the medication is very expensive. She was

started on 20 mg/day with weekly blood phenylalanine determinations. No change in her clinical condition occurred until dosage approached 60 mg/day. At that time the sertraline was gradually discontinued and the BH₄ was increased to 80 and then to 100 mg/day. On this dosage she has progressively improved over the period of a year to the point where she is off all psychotropic drugs and her depression has resolved. At present she is on a normal diet of her own choosing and the blood phenylalanine levels are usually between 360 and 480 $\mu\text{mol/liter}$. She has been able to take care of her child, and resumed daily care of the home in terms of meals and household chores.

DISCUSSION

There was discussion concerning dosage of BH₄ for this adult. Due to her obesity and the cost of BH₄, it was decided to see if she might respond to a smaller dose than the 20 mg/kg used in newborn screening to rule out BH₄ deficiency (1).

The cost of BH₄ is prohibitive and was not covered by insurance. In U.S. dollars, it costs \$5760 per year (list prices). This is about the same as the cost of the medical dietary products used at present for persons with PKU; however, it still is a significant financial burden. The clinical course of significant improvement of this individual coincided with BH₄ therapy, whereas her response to various psychotropic drugs prescribed by a psychiatrist were ineffectual. Consideration for trial of placebo treatment was entertained but this was unacceptable to the parents and the patient and so it was never carried out. An informed consent obtained at the initiation of treatment had not included a trial of placebo therapy and therefore it was considered to be unethical to institute it without consent. However, clinically, her improvement is without doubt. The use of BH₄ during pregnancy in women with mild hyperphenylalaninemia has not been evaluated to date but should be considered in special cases.

In summary, a 25-year-old woman with mild hyperphenylalaninemia due to a PAH mutation of IVS12nt1g→a/E390G has been treated for 1 year with BH₄ therapy. Maintenance dosage of only 100 mg/day has resulted in significant improvement of depression and panic attacks, with discontinuance of psychotropic medication. The cost of the BH₄ therapy presents a significant problem for this family due to refusal of the insurance company to cover the

cost of this treatment. A placebo effect could not be ruled out for ethical reasons.

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Received November 13, 2001, and in revised form November
26, 2001

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