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CASE REPORT

Dihydropteridine Reductase Deficiency and Treatment with Tetrahydrobiopterin: A Case Report

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Abstract Dihydropteridine reductase (DHPR) deficiency is a genetic disorder of tetrahydrobiopterin (BH4) regeneration and may present with hyperphenylalaninemia, microcephaly, hypotonia, mental retardation, and convulsions. BH4 is an essential cofactor for the hydroxylation of aromatic amino acids and a deficiency of BH4 results in decreased synthesis of dopamine and serotonin. We present a 27-month-old female patient with DHPR deficiency who was treated with L-dopa/carbidopa (2 mg/kg, four times per day), 5-hydroxytryptophan (2 mg/kg, four times per day), folinic acid (10 mg/day), and BH4 supplementation (20 mg/kg, twice a day). Although remarkable clinical improvement with normal plasma phenylalanine (Phe) levels and increased phenylalanine tolerance was noted 1 month after the treatment, CSF neurotransmitter metabolites did not improve. BH4 supplementation was increased to 40 mg/kg/day and the CSF study was repeated 1 month later. There was no significant change of CSF neurotransmitters, BH4 or BH2 levels but plasma Phe level was within normal range. Surprisingly, she had developmental improvement noted at 1-month and 3-month visits following an augmented neurotransmitter and BH4 treatment. She was able to pull herself to the standing position and sit down on her own. She was also noted to be more alert and responsive following treatment. Her expressive language did not improve, although her receptive language was markedly improved. The above treatment improved patient's clinical findings, normalized blood Phe levels, and increased Phe tolerance in the diet, but neither 20 nor 40 mg/kg/day BH4 supplementation corrected neurotransmitter or BH4 levels or increased BH2 level in CSF. Further studies are needed to find the optimal management plan for patients with DHPR deficiency.

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Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
5-MTHF	5-Methyltetrahydrofolate
BH4	Tetrahydrobiopterin
CSF	Cerebral spinal fluid
DHPR	Dihydropteridine reductase
HVA	Homovanillic acid
NO	Nitric oxide

Introduction

Dihydropteridine reductase (DHPR) deficiency (OMIM: 261630) is an autosomal recessive disorder in the regeneration pathway of tetrahydrobiopterin (BH4). Individuals with DHPR deficiency may present with hyperphenylalaninemia, microcephaly, hypotonia, mental retardation, and convulsions (Blau et al. 1996; Ponzone et al. 2004). DHPR

deficiency is encoded by the gene *QPDR* and missense mutations, insertions/deletions, and splice site mutations in the *QPDR* gene have been associated with DHPR deficiency (Dahl et al. 1987; Dianzani et al. 1998; Howells et al. 1990).

Although there is no curative treatment for DHPR deficiency, a low phenylalanine diet, L-dopa, and 5-hydroxytryptophan supplementation are the mainstay of treatment to keep phenylalanine levels within normal range and to increase the level of neurotransmitters. Folinic acid supplementation, which is also utilized as DHPR, is associated with the maintenance of appropriate folate levels, and patients with DHPR deficiency may have low folate (5-Methyltetrahydrofolate) levels in CSF (Irons et al. 1987; Smith et al. 1985). BH4 is not generally used to treat DHPR deficiency, as large quantities are required to normalize peripheral phenylalanine levels in the absence of the recycling enzyme (Kaufman et al. 1982). The effect of large dose BH4 on central amine metabolism and on CSF BH4 levels in DHPR deficiency has not been reported. In this report, we present a patient with DHPR deficiency who had significant clinical improvement after BH4 supplementation.

Case Report

The patient had elevated phenylalanine detected on newborn screening and was subsequently diagnosed with DHPR deficiency based on decreased activity of DHPR measured on a second newborn screening filter card. Molecular genetic analysis of the *QPDR* gene was performed in peripheral blood and revealed a novel homozygous splice site mutation (c.199-1g>t) consistent with the biochemical diagnosis of DHPR deficiency.

The patient presented to our institution at 27 months of age for further evaluation and treatment. Since initial diagnosis, she had been on a phenylalanine-restricted diet, folinic acid (3 mg/day), and L-dopa (1.4 mg/kg/day). She was reported to have global developmental delay, hypotonia, and convulsions for which she received levetiracetam in the past.

At her initial evaluation in our clinic, she had a mildly elevated plasma phenylalanine level of 170.4 (reference range 23–95 nmol/ml). Her protein intake was 2.5 g/kg and 44% (1.1 g/kg) of the protein was from an incomplete protein in the form of a metabolic formula (free of phenylalanine). Her total phenylalanine intake was 300 mg/day (approximately 25–30 mg/kg phenylalanine). The patient was unable to sit on her own or pull herself to a sitting position. She had minimal expressive or receptive language skills, although she was reported to react with familiarity toward her family members. She had a normal electroencephalogram.

We switched her from L-dopa (1.4 mg/kg/day) and folinic acid (3mg/day) to carbidopa/levodopa (25/100) 2 mg/kg/ day four times daily and folinic acid 10 mg/day. We also added 5-hydroxytryptophan (10 mg/mL) 2 mg/kg/day four times daily. After 2 weeks of this augmented neurotransmitter therapy, we also added sapropterin dihydrochloride (KUVAN), a derivative of BH4, at a dose of 20 mg/kg/day for 2 months. This dosage was then increased to 40 mg/kg/day. The patient had noted developmental improvement 1 month after initiation of BH4 supplementation. Although she remained hypotonic, she was able to pull herself to the standing position and sit down on her own. Her expressive language did not improve, although her receptive language was markedly improved. She was noted to be more alert and responsive after 1 month of treatment with high doses of BH4 supplementation (40 mg/kg/day). Throughout the 3 months of treatment, she was slowly weaned from incomplete protein source while simultaneously increasing complete protein sources. The patient was discharged with similar protein intake at 2.5 g/kg and no longer required an incomplete protein source (medical formula) with all of the protein coming from complete protein. The patient continued to increase her complete protein sources, including animal protein, and her phenylalanine levels remained below 120 nmol/ml.

Biochemical Results

CSF neurotransmitter metabolites and CSF amino acid analysis were performed three times: (1) 2 weeks after the augmented neurotransmitter therapy but prior to BH4 supplementation; (2) after 65 days on BH4 at 20 mg/kg/day; and (3) after 30 days on BH4 at 40 mg/kg/day. Despite BH4 supplementation and neurotransmitter therapy, tetrahydrobiopterin, 5-hydroxyindoleacetic acid, and homovanillic acid remained below reference ranges (Table 1). She had elevated dihydrobiopterin (BH2) before BH4 therapy. There was no significant increase in BH2 levels on BH4 supplementation; plasma phenylalanine level normalized and dietary phenylalanine tolerance increased on 20 mg/kg/day of BH4 therapy.

Discussion

Although BH4 supplementation may increase phenylalanine tolerance and lower plasma phenylalanine levels in patients with DHPR deficiency, the effectiveness of BH4 therapy in the correction of CSF neurotransmitter metabolites is not apparent. Nor is it clear if BH4 supplementation would increase levels of 7, 8-dihydrobiopterin (BH2), and increase further nitric oxide (NO) uncoupling and oxidative stress.

Table 1 Metabolites measured in plasma and cerebral spinal fluid (CSF) following treatment with sapropterin dihydrochloride (BH4)

		65 days BH4 (20 mg/kg)	30 days BH4 (40 mg/kg)	
Metabolite	Neurotransmitter therapy[a] Prior to BH4 supplementation	Neurotransmitter[b]+ BH4 (20 mg/kg/day) therapy	Neurotransmitter[b]+ BH4 (40 mg/kg/day) therapy	Reference ranges
5-MTHF, CSF	100	100	95	40–150 nmol/L
5-HIAA, CSF	23	8	18	74–345 nmol/L
HVA, CSF	108	100	137	233–928 nmol/L
3-O-methyldopa, CSF	201	616	292	< 150 nmol/L
Neopterin, CSF	15	10	9	7–65 nmol/L
Tetrahydrobiopterin, CSF	12	12	16	18–50 nmol/L
Dihydrobiopterin, CSF	28	31	27	2.2–13 nmol/L
Phenylalanine, CSF	34.8	133.9*	11	5–25 nmol/mL
Phenylalanine, plasma	170.5	75.5*	60.0	23–95 nmol/mL
Tyrosine, CSF	9.6	12.4	9.1	4–26 nmol/ml
Tyrosine, plasma	82.8	49.2	36.4	22–102 nmol/ml

5-MTHF 5-Methyltetrahydrofolate, *5-HIAA* 5-hydroxyindoleacetic acid, *HVA* homovanillic acid

*Plasma phenylalanine level was measured 1 week before CSF phenylalanine

[a] The patient was on folinic acid (10 mg), carbidopa/levodopa (2 mg/kg/day), and 5-hydroxytryptophan (2 mg/kg/day)

[b] The patient remained on folinic acid, carbidopa/levodopa, and 5-hydroxytryptophan

Isolated case reports have suggested that BH4 may cross the blood–brain barrier and have therapeutic potential for individuals with primary BH4 deficiency. Initial therapy with BH4 supplementation in two DHPR-deficient patients resulted in increased pterins (BH4 and 6-MPH4) in CSF suggesting that BH4 may cross the blood–brain barrier (Kaufman et al. 1982). Treatment with BH4 was reported in another individual with DHPR deficiency for 12 months without progression of neurologic symptoms suggesting that monotherapy with BH4 may be a sufficient treatment, although homovanillic acid and 5-hydroxyindoleacetic acid levels were decreased after discontinuation of neurotransmitter therapy (Ponzone et al. 1993). Animal studies have provided evidence that larger doses of BH4 supplementation result in elevated pterin concentrations in the brain and suggested that BH4 may enter the brain when appropriate dosage is utilized (Brand et al. 1996). A minimal dose of 20 mg/kg/day of BH4 may be required before changes in neurotransmitter metabolites are noted (al Aqeel et al. 1992; Kapatos and Kaufman 1981).

We present a patient with DHPR deficiency that was noted to have neurologic improvement after the initiation of BH4 supplementation, although neurotransmitter therapy was augmented with the addition of both carbidopa (the patient remained on L-dopa) and 5-hydroxytryptophan. The patient was trialed on 20 mg/kg/day and 40 mg/kg/day of BH4 supplementation. Plasma phenylalanine normalized from 170.5 to 75.5 nmol/mL (reference range 23–95 nmol/mL) with 20 mg/kg/day of BH4 supplementation and remained within the normal range when the dose of BH4 supplementation was increased (Table 1). She had elevated BH2 level in CSF and it did not increase on BH4 treatment. Despite clinical improvement after BH4 therapy and neurotransmitter supplementation, there were no significant changes in CSF neurotransmitter metabolites.

It is unclear whether the patient's clinical improvement was a result of BH4 supplementation or the initiation of L-dopa/carbidopa and 5-hydroxytryptophan. BH4 supplementation did improve the patient's phenylalanine tolerance and the patient was able to eat a regular diet. High doses of BH4 supplementation may be necessary to cross the blood–brain barrier and provide a therapeutic effect for individuals with an error in BH4 metabolism.

BH2 production is higher than normal in individuals with DHPR deficiency because of the enzyme defect. Some of the symptoms might be caused by increased BH2 levels and decreased BH4/BH2 ratio, which will result in NO uncoupling and increased production of superoxides. There is a concern that BH4 supplementation can further increase BH2 production, which will cause decreased BH4/BH2 ratio in patients with DHPR deficiency. On the other hand, one can speculate that BH4 supplementation may actually increase BH4 availability, which can function as a cofactor for hydroxylases, an electron donor to nitric oxide synthase, and improve NO coupling. In this case, we showed that BH4 treatment did not increase BH2 in CSF. Further

studies are needed to prove that BH4 supplementation does not decrease BH4/BH2 ratio further and find the optimal management plan for patients with DHPR deficiency.

Synopsis

A patient with DHPR deficiency was treated with high doses of BH4 supplementation resulting in clinical improvement despite limited improvement in CSF metabolites.

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Hyperphenylalaninemia, BH4-deficient, C; HPABH4C; 261630

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