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Case Report

L-Dopa Might Be Insufficient to Suppress Development of Prolactinomas in Dihydropteridine Reductase-Deficiency Patients

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Abstract

Dihydropteridine reductase (DHPR) deficiency is a disorder that prevents regeneration of tetrahydrobiopterin (BH4), causing hyperphenylalaninemia (HPA) and low levels of neurotransmitters, including dopamine. Due to low levels of dopamine, patients present with hyperprolactinemia. Treatment consists of a phenylalanine (Phe)-restricted diet, hydroxytryptophan and levodopa (L-Dopa) supplementation, leading to a rapid normalization of prolactin (PRL) levels. We report a case of a patient with DHPR deficiency presenting with new symptomatic hyperprolactinemia and amenorrhea in adolescence despite appropriate management. The prolactinoma was confirmed with pituitary magnetic resonance imaging. The patient was started on cabergoline with rapid normalization of PRL levels and resolution of symptoms, in keeping with previous reports. Cabergoline has a stronger affinity for the D2R receptor and longer half-life than L-Dopa, leading to lactotroph apoptosis, tumor shrinkage, and rapid and maintained normalization of PRL levels, with a better side-effect profile. Patients with DHPR deficiency need to be actively monitored for symptomatic hyperprolactinemia, as L-Dopa monotherapy is insufficient to suppress PRL secretion, leading to lactotroph hypertrophy and proliferation over time and development of prolactinomas in later life.

Key Words: DHPR, hyperprolactinemia, prolactinoma, cabergoline

Abbreviations: 5HIAA, 5-hydroxyindoleacetic acid; BH4, tetrahydrobiopterin; CSF, cerebrospinal fluid; DHPR, dihydropteridine reductase; HPA, hyperphenylalaninemia; HVA, homovanillic acid; L-Dopa, levodopa; MRI, magnetic resonance imaging; Phe, phenylalanine; PRL, prolactin; qBH2, quinoid form of dihydrobiopterin; RR, reference range.

Introduction

Dihydropteridine reductase (DHPR) deficiency is a disorder that prevents regeneration of tetrahydrobiopterin (BH4), causing hyperphenylalaninemia (HPA) and low levels of monoamine neurotransmitters. Patients present with global developmental delay, hypotonia, movement disorders, seizures, and microcephaly. Treatment consists of a phenylalanine (Phe)-restricted diet and increasing doses of levodopa (L-Dopa)/carbidopa and hydroxytryptophan. Monitoring plasma prolactin (PRL) during treatment reflects dopamine levels in the central nervous system due to its reverse inhibition. Patients initially present with high PRL concentrations that decrease quickly after starting treatment. We present a case of a patient with symptomatic hyperprolactinemia despite normalization of Phe and monoamine neurotransmitters that led to the diagnosis of a pituitary microadenoma.

Case Presentation

A 15-year-old female patient presented at age 3 months with oculogyric crisis and body stiffness. She was found to have HPA and a high serum PRL concentration.

Diagnostic Assessment

Subsequent cerebrospinal fluid (CSF) analysis revealed low BH4 7 nmol/L (0.126 µg/dL) (reference range [RR], 8-57 nmol/L; 0.144-0.9 µg/dL), homovanillic acid (HVA) 125 nmol/L (2.25 µg/dL) (RR, 154-867 nmol/L; 2.77-15.6 µg/dL), and 5-hydroxyindoleacetic acid (5HIAA) 30 nmol/L (0.54 µg/dL) (RR, 89-367 nmol/L; 1.62-6.61 µg/dL), with high dihydrobiopterin 74.2 nmol/L (13.3 µg/dL) (RR, 0.4-13.9 nmol/L; 0.07-2.5 µg/dL) and normal 5-methyl tetrahydrofolate 80 nmol/L (1.44 µg/dL) (RR, 45-160 nmol/L; 0.8-2.88 µg/dL).

Enzyme assay showed low activity of DHPR reductase, and genetics confirmed the presence of a homozygous pathogenic variant c.53G > A p. (Gly18Asp) in the QDPR gene.

Treatment

The patient was started on treatment with 5-hydroxytryptophan and 10 mg/kg/day L-Dopa/carbidopa with normalization of 5HVA and 5HIAA in the CSF, leading to a rapid decrease in plasma PRL concentrations, that were maintained between 148 and 1430 mU/L (6.95-67.21 µg/L) (RR, 128-702 mU/L; 6.01-32.99 µg/L).

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Outcome and Follow-up

At age 14 years, she developed secondary amenorrhea. There was no history of headache, vision impairment, or galactorrhea, and prior to developing amenorrhea, she had been having regular periods for 5 years. She demonstrated significant hyperprolactinemia (>7000 mU/L; >329 µg/L) despite good compliance with treatment as shown by her Phe levels and CSF neurotransmitters.

Secondary causes of amenorrhea were ruled out and brain magnetic resonance imaging (MRI) showed a lesion in her pituitary gland consistent with a microadenoma (largest 5 mm on coronal view and 1 mm on sagittal view) (Fig. 1). She was started on low-dose cabergoline (0.25 mg/weekly) with rapid normalization of PRL levels and a reversal of symptoms.

Discussion

DHPR deficiency (OMIM No. 261630) is the second most frequent disease among BH4 synthesis and regeneration disorders (BH4-deficient disorders), comprising 33% of them. It is an autosomal recessive disease caused by mutations in *QDPR* gene, which results in impaired DHPR activity and low plasma levels of BH4, leading to impaired hepatic conversion of Phe to tyrosine. In addition, dopamine and serotonin synthesis are impaired due to a lack of tyrosine and tryptophan hydroxylase activity [1–3]. (Fig. 2). Biochemical confirmation is achieved by analyzing urinary pterins, CSF neurotransmitters (low 5-HIAA and HVA), and dried blood-spot DHPR activity. Treatment aims to lower Phe levels and increase levels of depleted neurotransmitters. Patients follow a Phe-restricted diet for life, with regular monitoring of Phe concentrations in dried blood spots. In addition, they receive treatment with increasing doses of L-Dopa (the immediate precursor of dopamine), carbidopa, and 5-hydroxytryptophan.

There is no clear consensus on how to monitor treatment response in these patients [3]. Regular lumbar punctures with CSF HVA and 5-HIAA analysis as markers for dopamine and serotonin turnover, respectively, can be used for drug dose titration or for clarification of unexplained symptoms (especially in younger children, for whom the spectrum of neurological symptoms can be broader) [1, 2]. However, due to the invasiveness of repeated lumbar puncture and reduced availability of these laboratory tests, serum PRL has been proposed as a less invasive way of monitoring treatment response.

PRL is a polypeptide hormone secreted by lactotrophs in the anterior pituitary gland, which promotes lactation and breast development. Its production is regulated by both negative feedback from dopamine and promoting dopamine release [4, 5].

Production of dopamine in the hypothalamic arcuate nucleus leads to inhibition of PRL gene expression, lactotroph cell proliferation [6], PRL secretion [7, 8], and induces lactotroph apoptosis [9] by acting on dopamine receptors (D2Rs) in the anterior pituitary. In mice, persistent suppression of dopamine secretion causes lactotroph hyperplasia, pituitary gland enlargement, and multifocal prolactinomas [10].

The short and long isoforms (D2S and D2L) of D2R are produced by alternative splicing [6] and are hypothesized to have specific roles in the mitogen-activated protein kinase pathways regulating PRL production from lactotrophs [10]. Mice overexpressing D2S have a reduced pituitary size and PRL concentrations compared to wild-type or D2L-overexpressing mice [11]. These observations suggest that dopamine suppresses lactotrophs via the D2S receptor isoform [12]. Furthermore, pituitary D2L expression is much lower than that of D2S [13].

Despite the known role of D2R in PRL regulation, many studies have suggested that other receptors may participate in the process, in particular in lactotroph apoptosis [12]. Thus, the complexity of treatment of dopamine-deficient hyperprolactinemia may not be as straightforward as replacement of dopamine.

Hyperprolactinemia at diagnosis of dopamine-deficient metabolic conditions such as DHPR deficiency normally responds well to dopamine replacement with L-Dopa [1, 2]. Theoretically, adequate dopamine replacement should overcome the lack of dopamine suppression on lactotrophs, hence preventing hyperprolactinemia.

However, there have been reported cases of patients developing hyperprolactinemia (>1000 mU/L; >47 µg/L), with some found to have associated prolactinomas at a later age despite adequate or even high-dose L-Dopa replacement [14–16]. One study demonstrated 42% of the adolescent and adult population with a BH4-deficient disorder had high PRL concentrations, which were aggravated by menstrual cycles [14]. Perhaps the current recommended treatment at diagnosis is sufficient only to treat the symptoms, but it is inadequate for dopamine function, as it does not effectively suppress PRL production or inhibit lactotroph proliferation. Thus, we postulate

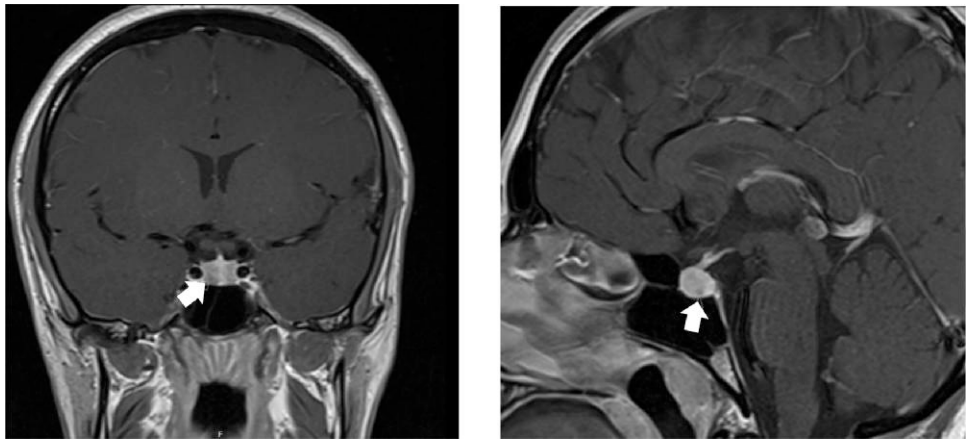

Figure 1. Coronal (left) and sagittal (right) views of brain magnetic resonance imaging, T1-weighted sequences. A small focus of hypointensity post contrast administration is noted in the right inferior aspect of the anterior pituitary gland (marked by arrows), consistent with a microprolactinoma.

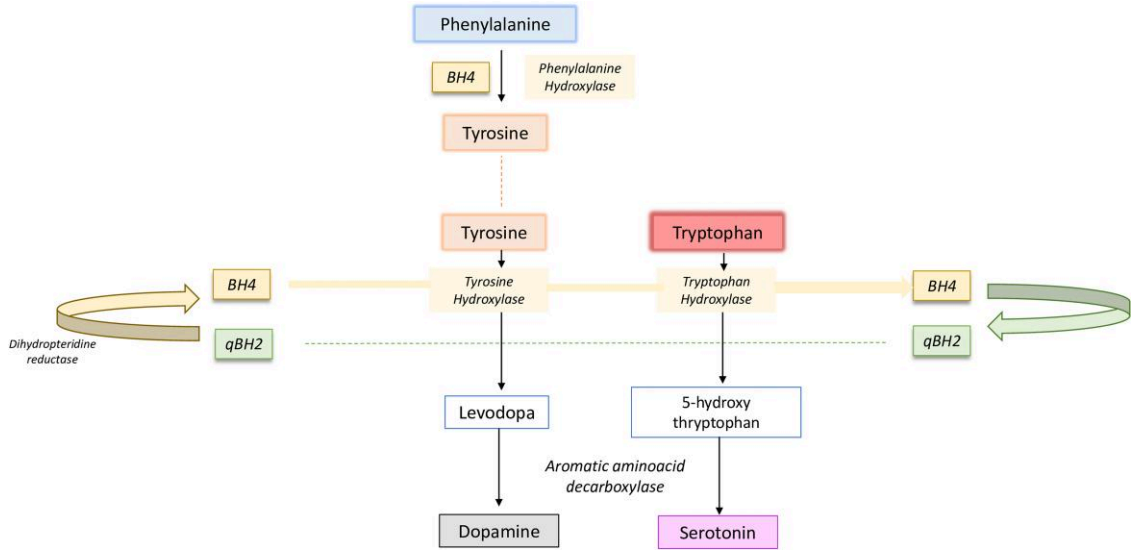

Figure 2. Pathway of metabolism of phenylalanine, tyrosine, and monoamines. BH4, tetrahydrobiopterin; qBH2, quinoid form of dihydrobiopterin.

that short-acting L-Dopa does not lead to adequate D2R-mediated suppression of PRL compared with longer-acting agonists such as cabergoline.

MRI and computed tomography brain imaging have found a variety of normal and abnormal findings in BH4-deficient disorders at diagnosis. Abnormal neuroradiological findings include brain atrophy, basal ganglia calcifications, white-matter changes, ventricular dilatation, areas of hypodensity, and global demyelination [1]. To date, no radiological hypothalamus-pituitary axis anomalies have been reported at diagnosis. Thus, this makes the subsequent finding of pituitary adenomas more likely due to a secondary cause. However, dedicated pituitary imaging is not part of routine brain imaging in BH4-deficient disorders and thus small pituitary lesions may be missed. Routine neurological imaging is also not a diagnostic requirement for BH4-deficient disorders according to international consensus [1]. However, based on published literature, including our case described here, there should be a low threshold for dedicated pituitary neuroimaging to look for adenomas if there is unexplained hyperprolactinemia despite optimizing dopamine replacement.

Bromocriptine and cabergoline are the 2 main drugs for prolactinomas, with cabergoline being preferred due to having a stronger affinity for D2R, a longer half-life (60 hours), and a better side-effect profile. Binding to D2R leads to decreased PRL secretion and lactotroph apoptosis, and thus tumor shrinkage [14].

Unsurprisingly, our case is in keeping with the previously published literature, which has shown that cabergoline is effective in reducing hyperprolactinemia in BH4-deficient disorders.

Notably, it has also been reported that if the same L-Dopa dose was given more frequently, better control of hyperprolactinemia would be achieved [16]. This suggests that standard L-Dopa may not achieve the steady state required for consistent PRL suppression vs long-acting agents such as cabergoline. Thus, we postulate that a consistent level of dopamine over 24 hours may be required to suppress the lactotroph's proliferation and function.

Another case series reported that diurnal PRL profiles measured in 2 patients showed reduced PRL fluctuations with the addition of pramipexole to L-Dopa monotherapy [17]. This further supports the hypothesis that in BH4-deficiency disorders, L-Dopa monotherapy is insufficient to suppress PRL secretion and leads to lactotroph hypertrophy and proliferation over time and the development of prolactinomas in later life.

A better understanding of the pathophysiology of hyperprolactinemia secondary to dopamine-deficient metabolic conditions and the precise mechanism of prolactinoma development is greatly needed, especially considering that different pharmacological compounds act on lactotroph cells through different molecular pathways.

Learning Points

- Hyperprolactinemia in patients with BH4-deficient disorders, such as DHPR deficiency, does not always reflect suboptimal treatment and should warrant further investigations, including a pituitary MRI.
- Close monitoring for symptoms of hyperprolactinemia (oligomenorrhea/amenorrhea, galactorrhea) is needed.
- L-Dopa might not be sufficient to suppress hyperprolactinemia and development of prolactinomas in DHPR-deficiency patients. Using cabergoline reverses symptoms and normalizes PRL levels effectively, due to having a stronger affinity for dopamine receptors and a longer half-life.

Contributors

U.D.M., D.P., and C.G.G. contributed to the manuscript writing. U.D.M. created the figures and submitted the manuscript. S.B and H.W.G. were involved in the diagnosis and management of the patient, and manuscript review. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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