Target Prolactin Range in Treatment of Tetrahydrobiopterin Deficiency

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The introduction of dopamine agonists for treating tetrahydrobiopterin deficiency imposes the evaluation of peripheral prolactin as the sole reliable biochemical marker of dopaminergic homeostasis. Here we provide the clinical interpretation of the previously described short prolactin profile, based on the longitudinal monitoring of 8 patients with tetrahydrobiopterin deficiency. *(J Pediatr 2016;168:236-9).*

Disorders of synthesis and regeneration of tetrahydrobiopterin (BH4), the natural cofactor of aromatic amino acid hydroxylases, lead to impairment of serotoninergic and catecholaminergic neurotransmission and are characterized by motor dysfunction, intellectual disability, impaired muscle tone, movement disorders, and epileptic seizures. Although the outcomes of BH4 deficiencies are highly variable, early diagnosis and treatment increase the chance of better prognosis.

Phenylalanine restricted diet, synthetic BH4, and neurotransmitter replacement therapy with 5-hydroxytryptophan and L-3,4-dihydroxyphenylalanine (L-Dopa) are the cornerstone of treatment aimed at preventing irreversible brain damage and even death from the earliest perinatal period.[1] Like in Parkinson's disease, L-Dopa therapy in children becomes increasingly troublesome after the first few years of age, when higher doses are necessary and adverse effects may become prominent. Despite dose fractionation and use of L-Dopa sparing drugs, wearing-off-, end-of-dose-phenomena, and dyskinesias invariably complicate the clinical picture.[2-5] Substantial advantages have been recently obtained by the introduction of dopamine-agonists as an adjunct to L-Dopa therapy.[6,7]

Monitoring and optimization of treatment in BH4 deficiency traditionally relied on clinical evaluation and periodical measurements of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF).

Dopamine is the physiological inhibitor of prolactin (PRL) incretion, through a direct effect on the anterior pituitary lactotrophs. As a consequence, dopamine deficiency due to disorders of BH4 metabolism invariably results in peripheral hyperprolactinemia. During the last years, we demonstrated a negative correlation between dopamine and PRL concentrations, which avoided the use of repeated lumbar punctures to monitor dopaminergic homeostasis in BH4 deficiency.[8]

Since the introduction of dopamine agonists in BH4 deficiency, this indirect tool gained an exquisite relevance for biochemical monitoring of these patients, and the measurement of CSF HVA proved to be unreliable as not reflecting the whole dopaminergic tone. To facilitate the practice of PRL testing, we showed that the analysis of a short PRL profile was suitable in clinics.[9] In this article, we report on the longitudinal monitoring of BH4 deficiency with this procedure, also providing the target PRL range associated with the best clinical outcome of patients.

BH4	Tetrahydrobiopterin
CSF	Cerebrospinal fluid
HVA	Homovanillic acid
L-Dopa	L-3,4-dihydroxyphenylalanine
PRL	Prolactin
UPDRS	Unified Parkinson's Disease Rating Scale

Methods

The clinical and biochemical features of 8 patients suffering from severe BH4 deficiency (5 with 6-pyruvoyl tetrahydropterin synthase deficiency, 3 with dihydropteridine reductase deficiency), followed at our department were previously described.[9] Besides diet or BH4 administration, all patients were on neurotransmitter replacement therapy. Such a therapy was differently personalized during the last 5 years after the introduction of a dopamine agonist (pramipexole; Boehringer Ingelheim Pharma GmbH & Co, Ingelheim am Rhein, Germany) and was adjusted according to weight, clinical picture, and biochemical assessments.[1]

We present here the outcome of 75 unique and previously unpublished short PRL profiles compared with patients' concurrent clinical picture. Peripheral PRL was measured by a fluorometric immunoassay in 3 samples collected just before the L-Dopa and/or dopamine agonist in the morning, 3 hours after the first sample, and 6 hours after the first sample.[9] In each patient, the collected PRL profiles (ranging from 2 to 12) were related to the clinical picture, also assessed by using an adapted Unified Parkinson's Disease Rating Scale (UPDRS).[6,7] The study was approved by the ethical standards committee. Written informed consent was obtained from all patients or parents.

Results

Three different types of short PRL profiles were evidenced in relation with patients' clinical response to the therapy

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(Figure). Profiles of patients not yet receiving dopamine agonists but only classical L-Dopa therapy (7.5 ± 2.4 mg/kg/d in 3 doses) fluctuated from severe hyperprolactinemia at time 0 to even normal values at subsequent times (Figure, A), and none of them showed normal PRL concentration at time 0. A highly fluctuant clinical picture was characteristically associated with this profile, with prominent tremors, dyskinesia, or end-of-dose-phenomena (n = 11, adapted UPDRS 25 ± 12/135 ± 34).

A steadier and more satisfactory clinical picture (n = 55, adapted UPDRS 13 ± 6/135 ± 33) was associated with mild hyperprolactinemia (400-900 mU/L) at time 0 and normal PRL levels at 3 and 6 hours after treatment assumption (Figure, B). This type of PRL profile was obtained in patients receiving L-Dopa + pramipexole at doses of 4.5 ± 1.4 mg/kg/d and 0.014 ± 0.002 mg/kg/d in 2 administrations, respectively.

Patients showing normal PRL concentration at time 0, all receiving L-Dopa (4.7 ± 1.0 mg/kg/d) and pramipexole (0.031 ± 0.001 mg/kg/d) invariably developed symptoms of dopaminergic over-stimulation after a variable period of good clinical compensation (n = 9, adapted UPDRS 13 ± 6/133 ± 38), likely due to pramipexole over-dosage (Figure, C). Late clinical symptoms associated with this third profile included dystonia, dyskinesia, sleep disturbances, and a tendency to gambling. No differences in short serum PRL profile pattern were detected between patients suffering from 6-pyruvoyl tetrahydropterin synthase deficiency or dihydropteridine reductase deficiency (Tables I and II; Table II available at www.jpeds.com).

Discussion

The achievement of a correct L-Dopa replacement therapy in BH4 deficiency has been complicated for a long time by the rarity of these disorders and the continuous need of individual treatment adjustments since the neonatal period. Repeated clinical assessment and CSF HVA measurement were the best methods for monitoring patients. We showed that peripheral PRL measurement can be an objective, simple, noninvasive biochemical tool to integrate the clinical approach, as overlapping symptoms may be shared by over- and under-treated patients.[8] The introduction of dopamine agonists definitely improved the patients' outcome.[6,7] As the measurement of CSF HVA is not suitable where L-Dopa is not the sole replacement therapy, a short PRL profile was suggested as an indirect indicator of the whole dopaminergic tone, either due to L-Dopa or dopamine agonist effects.[9]

We provide the interpretation of a standardized PRL profile in light of the associated patients' clinical outcome. Such interpretation is especially useful for the prospective optimization of dopaminergic treatment in BH4 deficiency. Three significant types of PRL profiles could be identified. The

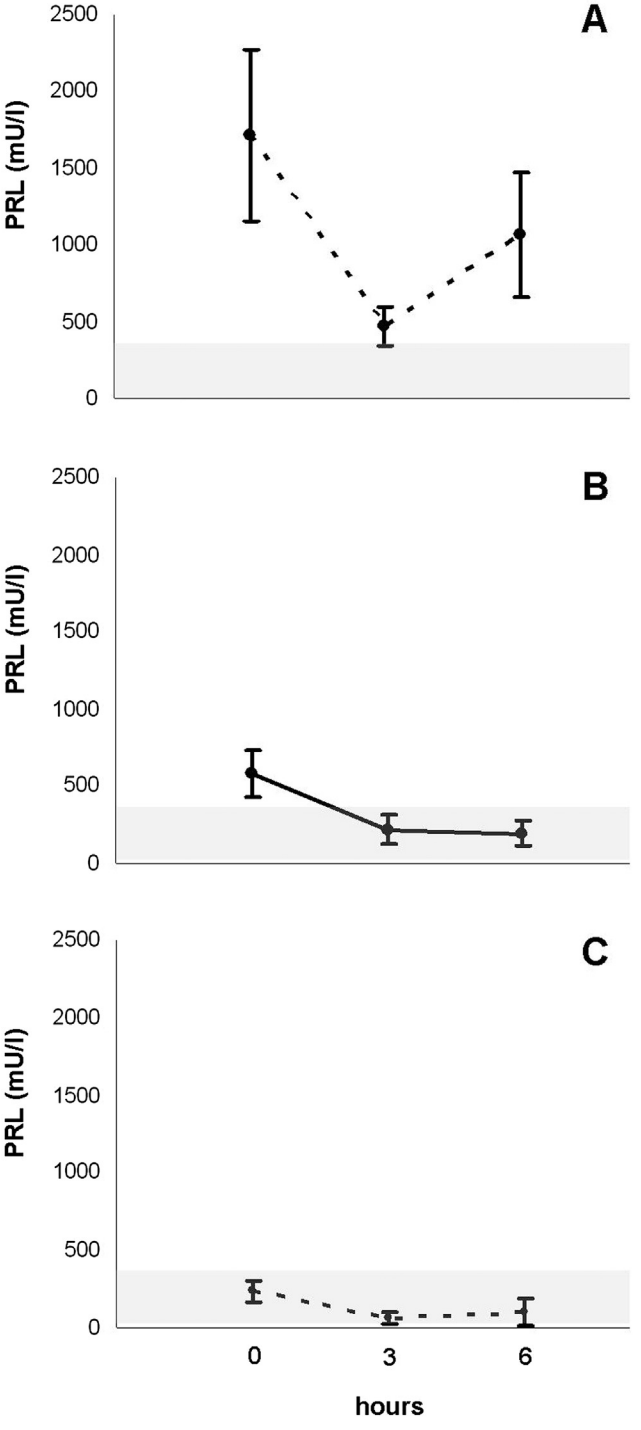

Figure. Outcomes of the short PRL profile in 8 patients with BH4 deficiency and clinical response to therapeutic regimen. **A,** The under-stimulation profile is observed in patients receiving traditional L-Dopa therapy associated with L-Dopa extenders. **B,** The optimal-stimulation profile represents the target PRL range in patients receiving L-Dopa + pramipexole therapy. **C,** The over-stimulation profile is associated to long-term adverse effects, likely due to pramipexole over-dosage. The *gray area* represents the normal PRL range.