Official Journal of the European Paediatric Neurology Society

Orginal article

Short prolactin profile for monitoring treatment in BH4 deficiency

Francesco Porta[*], *Alberto Ponzone*, *Marco Spada*

Department of Pediatrics, University of Torino, Piazza Polonia 94, 10126, Torino, Italy

ARTICLE INFO

Article history:
Received 2 December 2014
Received in revised form
22 January 2015
Accepted 28 January 2015

Keywords:
BH4 deficiency
Prolactin
L-dopa
Dopamine agonists
Parkinsonism

ABSTRACT

Tetrahydrobiopterin (BH4) deficiency causes hyperphenylalaninemia and impaired synthesis of serotonin and dopamine, leading to brain degeneration and early death if left untreated. Replacement therapy with neurotransmitters precursors is the cornerstone of treatment, relying on 5-hydroxytryptophan and L-dopa administration. Effective restoration of dopaminergic activity is thickened, like in Parkinson's disease, by the pulsatile pharmacokinetic profile of L-dopa. Monitoring of L-dopa therapy in BH4 deficiency is generally based upon clinical observation and periodical measurement of homovanillic acid (HVA) concentration in the cerebrospinal fluid (CSF). According to the finding that dopamine is the natural inhibitor of prolactin (PRL) incretion, we introduced the use of peripheral PRL measurement as an index of dopaminergic homeostasis, so avoiding the need of repeated lumbar punctures in patients with BH4 deficiency. As a single PRL evaluation can be misleading, due to the dependency of PRL fluctuations on L-dopa administration schedule, here we show that a short PRL profile is suitable for monitoring these patients. Together with the assessment of patients' clinical symptoms, this standardized tool will ensure an objective non-invasive reference to the management of dopaminergic replacement therapy in BH4 deficiency, even in patients treated with dopamine agonists.

1. Introduction

Tetrahydrobiopterin (BH4) is the natural cofactor for the enzymatic hydroxylation of phenylalanine, tyrosine and tryptophan, and for nitric oxide synthase. Five molecular defects responsible for inherited BH4 deficiency have been so far recognized, involving the cofactor biosynthesis and regeneration. The most common (60% of cases) is the deficiency of the enzyme 6-pyruvoyl tetrahydropterin synthase (PTPS; MIM 261640), required for the second step in the biosynthesis of BH4, followed by dihydropteridine reductase (DHPR) deficiency (30% of cases), the key step of BH4 regeneration.[1] These disorders cause hyperphenylalaninemia and impaired synthesis of serotonin and dopamine, leading to brain degeneration and early death if not promptly treated soon after birth.[2,3]

Differently from phenylketonuria,[4–6] the administration of synthetic BH4 is effective at the peripheral level in BH4 deficiency, so avoiding the need of a phenylalanine-restricted diet. Scarce effects, however, can be obtained at the central level,

* *Corresponding author*. Tel.: +39 011 6637777; fax: +39 011 3135382.
E-mail addresses: porta.franc@gmail.com (F. Porta), fporta@unito.it (A. Ponzone), marco.spada@unito.it (M. Spada).
http://dx.doi.org/10.1016/j.ejpn.2015.01.010

due to the poor brain entrance of exogenous BH4 across the blood brain barrier. Consequently, patients with severe BH4 deficiency additionally do require an appropriate and individualized neurotransmitters replacement therapy, traditionally relying on the fractionate administration of their hydroxylated precursors, 5-hydroxytryptophan (5-OH Trp) and L-dopa.[1]

Serotonin deficiency is generally well tolerated, and easily corrected by the administration of 5-OH Trp. On the contrary, the restoration of dopaminergic activity is complicated, like in Parkinson's disease, by the pulsatile pharmacokinetic profile of L-dopa, owing to its short half-life and erratic gastrointestinal absorption. Monitoring of L-dopa therapy in BH4 deficiency is generally based upon the clinical observation and the periodical measurement of homovanillic acid (HVA), a dopamine metabolite, in the cerebrospinal fluid (CSF).[7]

Based on the physiological concept that prolactin (PRL) incretion is inhibited by dopaminergic tone, we previously worked out an indirect tool for monitoring dopaminergic homeostasis through the assessment of plasma PRL, so avoiding repeated lumbar punctures for monitoring BH4 deficiency.[8] Single PRL evaluations, however, may be unreliable to this purpose, due to the large dependency of PRL concentration on the dopamine replacement schedule.[9] Likewise, the evaluation of HVA concentration in the CSF is unsuitable when treatment is implemented with dopamine agonists, allowing consistent curtailment of L-dopa therapy.[10,11]

To avoid these biases, we recently introduced the evaluation of the 24-h PRL profile for monitoring the biochemical effects of pramipexole (a non-ergot dopamine agonist) as an adjunct to L-dopa therapy in different forms of BH4 deficiency.[10,11] Here we describe a simplified method, similarly informative and suitable for patients' monitoring in the clinical setting.

2. Materials and methods

Nine patients with BH4 deficiency (5 affected by severe PTPS deficiency, 1 by mild PTPS deficiency, and 3 by DHPR deficiency) were prospectively followed for the evaluation of adequacy of their actual personalized therapeutic regimen. Patients' characteristics are reported in the Table 1.

Besides regular clinical evaluations (temporarily defined according to patients' age), a simplified 6-h PRL incretion profile protocol was applied to each patient. Peripheral PRL was measured by fluorometric immunoassay in three samples collected at 3-h time interval. The first sample was collected just before the dose therapy administration in the morning.

Given the significant negative correlation between peripheral PRL and CSF HVA ($r = -0.76$; $p < 0.05$) evidenced from previous published[8] and unpublished personal observations in BH4 deficient patients on L-dopa therapy, the CSF HVA concentrations were calculated on the basis of measured PRL concentrations in the three patients on conventional treatment.

3. Results

At each time, PRL concentrations were lower in patients receiving pramipexole with respect to those on conventional

Table 1 – Clinical data and treatment of 9 patients affected by tetrahydropterin (BH4) deficiency.

Patient	Age at diagnosis	Enzyme activity in RBC	Enzyme activity in fibroblasts (μU/mg)	Mutant alleles	Actual age (years)	Treatment						
						BH4 (mg/kg/day)	L-dopa (mg/kg/day)	Carbidopa (mg/kg/day)	5-OH-tryptophan (mg/kg/day)	Selegiline (mg/kg/day)	Entacapone (mg/kg/day)	Pramipexole (mg/kg/day)
		PTPS[a]	PTPS									
1 (○)	11 months	<0.1	<0.01	T76M/D136V	31	2.6	9.8	2.4	4.0	0.17	12.1	–
2 (●)	5 months	<0.1	<0.01	ΔV57/Δ(K29-32)	27	3.2	6.0	1.5	2.5	0.16	12.0	0.009
3 (■)	2 months	<0.1	<0.01	P87L/P87L	16	3.2	4.8	1.1	5.0	0.12	9.5	0.010
4 (▲)	21 days	ND	0.06	N52S/N52S	13	4.4	4.2	1.1	2.0	0.10	8.7	0.015
5 (Δ)	8 days	ND	ND	N52S/N52S	7	4.7	3.4	0.9	4.1	0.15	11.3	0.011
6 (●)	1 months	0.1	ND	K129E/K129E	30	–	–	–	–	0.09	–	–
		DHPR[b]										
7 (×)	14 days	<0.01	–	L14P/L14P	9	Diet	3.3	0.7	5.0	0.25	–	0.013
8 (+)	14 days	<0.01	–	G23D/Y150C	24	5.6	2.3	0.6	1.9	0.07	9.0	0.010
9 (▫)	11 months	<0.01	–	H158Y/H158Y	31	Diet	4.6	1.1	4.6	–	–	–

[a] PTPS activity in red blood cell: μU/gHb.
[b] DHPR activity in red blood cell: nM reduced ferricytochrome C/minute/5 mm disk.