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Different Strategies in the Treatment of Dihydropteridine Reductase Deficiency

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Introduction

Inherited deficiency of dihydropteridine reductase (DHPR, EC 1.66.99.7) impairs the regeneration of tetrahydrobiopterin (BH_4), the essential cofactor of phenylalanine (Phe), tyrosine (Tyr), and trypthophan (Trp) hydroxylases, which is oxidized to qBH_2 during a coupled reaction with these enzymes (1). Hyperphenylalaninemia and scarce production of monoamine neurotransmitters derived from Tyr and Trp-dopamine, norepinephrine, and serotonin-are the main metabolic derangements caused by DHPR deficiency. Untreated patients early develp a severe an progressive neurological picture, which is shared by other inborn errors of BH_4 metabolism (1). The control of hyperphenylalaninemia and biogenic amine deficiency is necessary to improve their prognosis, together with folinic acid supplementation to avoid folate depletion (2).

DHPR deficiency, however, is a heterogeneous disease both at clinical and molecular level. The dietary tolerance to Phe is higher than in classical phenyketonuria, but shows interindividual differences, as well as age-dependent increase (1). The control of hyperphenylalaninemia can be achieved either by a Phe-restricted diet or by administration of synthetic cofactor. As in these patients some recycling of BH_4 do occur (3), a daily dosage of 8-20 mg/kg is sufficient to attain normal serum Phe levels.

Despite substantial amounts of peripherally administered BH_4 can be found in cerebrospinal fluid (CSF), only some patients respond at the central level to BH_4 monotherapy (3,4). Most patients need neurotransmitter substitutive therapy, which can be realized by administering the hydroxylated precursors, l-Dopa and 5-OH-Trp, in conjunction with an inhibitor of peripheral amino acid decarboxylases. Also the daily doses and the number of administrations of neurotransmitter precursors have to be individually adjusted. Random fluctuations in response to this therapy are observed, especially when larger doses of l-Dopa are required, which can be obviated by the addition of a monoamine oxidase inhibitor (5).

As a consequence, the best choice of treatment must be thoroughly searched for in every patient affected by DHPR deficiency, as in the case here reported.

Case Report and Methods

Patient F.M., female, was born at term after an uncomplicated pregnancy as the first child of unrelated parents. Routine Guthrie testing on day 4 showed slightly elevated blood Phe concentration (4 mg%) which increased up to 37 mg% on a formula diet within the first month. Since then the infant was put on a Phe-restricted diet, but at the age of 4 monthes she developed hypertonic crises, lethargia, and oculogiric crises. DHPR deficiency

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Table 1. Clinical and biochemical monitiring in a patient affected by dihydropteridine reductase deficiency during different treatments. Phe=phenylalanine; Tyr=tyrosine; Trp=tryptophan; CSF=cerebrospinal fluid; 5-HIAA=5-hydroxyndole acetic acid; HVA=homovanillic acid; BH_4=tetrahydrobiopterin; nd=not done.

Treatment	Age	Clinical symptoms	Serum (umol/l)		CSF (nmol/l)			
			Phe	Tyr	5-HIAA	5-OH-Trp	HVA	l-Dopa
Diet only	5 mo	Lethargia Hypertonic crises Oculogiric crises Marked truncal hypotonia	378	91	16	nd	128	nd
Diet BH_4(6 mg/kg/day) 5-OH-Trp (2.5 mg/kg/day) l-Dopa (3.3 mg/kg/day)	7 mo	Lethargia Oculogiric crises Truncal hypotonia	180	85	72	nd	474	nd
Diet 5-OH-Trp (5 mg/kg/day) l-Dopa (5 mg/kg/day)	8 mo	Oculogiric crises Reduced truncal hypotonia	170	37	156	219	237	17
BH_4monotherapy (20 mg/kg/day)	9 mo	Lethargia Oculogiric crises Marked truncal hypotonia	52	43	28	1	173	4
Dict l-Deprenyl (0.25 mg/kg/day) 5-OH-Trp (5 mg/kg/day) l-Dopa (5 mg/kg/day)	9 mo	No symptoms	128	32	128	225	216	54

was ascertained at 5 months by enzyme activity measurement on blood spot, urinary pterin and CSF analysis, and combined Phe-BH_4 loading test (6).

Four different therapeutic strategies were then sequentially applied (BH_4 and neurotransmitter therapy at low doses; diet plus neurotransmitter therapy; BH_4 monotherapy; diet plus neurotransmitter therapy plus monoamine oxidase inhibitor), and monitored either clinically or biochemically (Table 1).

Serum and CSF samples were taken half way between two successive drug administrations. Serum Phe and Tyr were measured chromatographically with a Kromakon 500 automatic analyzer. CSF concentrations of homovanillic acid (HVA), 5-hydroxyndole acetic acid (5-HIAA), and l-DOPA were measured by HPLC with an ESA Coulochem 5100A eletrochemical detector.

Results and Discussion

Monitoring of treatment in BH_4 deficiency can be implemented either clinically, by evaluating the minimal dose effective in relieving symptoms of biogenic amine deficiency, or biochemically, by measuring the CSF concentration of neurotransmitter metabolites, besides the level of blood Phe and Tyr (2,7). Pitfalls in clinical monitoring are due to the fact that dopamine and serotonin can produce agonist and antagonist effects, which can also mimic the symptoms of deficiency (2,8). On the other hand, a good clinical result can be achieved in these patients at CSF levels of HVA and of 5-HIAA below those of age-matched controls (9).

Data shown in Table 1 suggest that the CSF concentration of l-DOPA and of 5-OH-Trp are more tightly related to the clinical picture. BH_4 was shown to be peripherally effective in the control of hyperphenylalaninemia in this patient; at the central level, however, the effect was very poor, even at high cofactor doses, on the basis of both clinical and biochemical evaluation.

As previously reported in cases of 6-pyruvoyl tetrahydropterin synthase and of DHPR deficiency (5,10,11) the optimal results were obtained by the addition to the classical treatment of l-Deprenyl, a selective monoamine oxidase B inhibitor. It should be noted, finally, that on such a therapy the significance of CSF HVA and 5-HIAA concentration is lessened because of the limiting effect of l-Deprenyl on dopamine and serotonin degradation.

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