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Short Communication

Deprenyl in 6-Pyruvoyl Tetrahydropterin Synthase Deficiency

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Introduction

Outcome and prognosis of patients suffering from 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency are strictly dependent on the control of hyperphenylalaninemia and biogenic amine deficiency. While the former can be easily normalized by a phenylalanine restricted diet or by synthetic tetrahydrobiopterin (BH_4) administration, adequate dopamine and serotonin supply is hampered by a number of drawbacks. Only a few patients respond to BH_4 monotherapy by increasing their monoamine production at the central level, while most patiemts have to be given neurotransmitter substitutive therapy, individually adjusted as for the daily dose and the number of administrations (1). Random fluctuations in motor and cognitive performances may appear in patients on neurotransmitter therapy, especially when larger doses of 1-Dopa are required, owing to interference of neurotransmitter precursor and phenylalanine metabolism (2) or to plasma dopamine fluctuations related to the short 1-Dopa half-life (3).

Recently, we pointed out in two patients with unsatisfactory response to a classical treatment that therapeutic inadequacy was corrected by the concurrent administration of 1-Deprenyl (selegiline, phenylisopropylmethylpropynilamine), a selective, irreversible inhibitor of monoamine oxidase B (4). Three additional patients with PTPS deficieny were subsequently treased and results are here reported.

Patient Selection and Treatment

Five patients suffering from different forms of PTPS deficiency were included in this study. Four of them were followed in Torino and one in Budapest. A definite diagnosis was obtained by the analysis of urinary pterins, the measurement of enzyme activity in red biood cells, and by a BH4 loading test. CSF levels of homovanillic acid (HVA) and of 5-hydroxyndole acetic acid (5-HIAA) were measured before and after therapy. As shown in Table 1, four patiens (cases 1-4) belonged to the classical type of the disease, while the fifth was affected by a partial PTPS deficiency. All patients but one (case 5, T.G.) had been treated following the current approach with BH4, 1-Dopa, 5-OH-Trp plus carbidopa (1:10 to 1-Dopa) at the doses reported in Tabe 2. Cases 1 and 2 were poorly responsive to the therapy, cases 3 and 4 were good responders, though erratic symptoms of biogenic amine deficiency reappeared, generally late in the afternoon (Table 2). Case 5 had been treated for the first three years of life with cofactor therapy alone (2.4 to 4.9 mg/kg body weight per day) because of persistent hyperphenylalaninemia with normal CSF neurotransmitter metabolites. Afterwards, this "peripheral" phenotype reverted to a "central" phenotype, with normal serum phenylalnine on free diet, and progressive reduction of CSF biopterin, HVA, and 5-HIAA concentrations (5). However, this girl had always been symptom free, with normal physical, intellectual and motor development. All patients were given 1-Deprenyl at the dose of 0.25 mg/kg body weight per day, in a single oral administration, in

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Table 1. Clinical and biochemical data of five PTPS deficient patients enrolled in treatment with 1-Deprenyl

Patients	Clincal phenotype	Age	CSF neurotransmitter metabolite levels (nmol/L)*			
			at diagnosis		on classical treatment	
			HVA	5-HIAA	HVA	5-HIAA
1. M.T.	classic	4.5 yr	=	=	421	163
2. I.A.	classic	9 yr	34	13	288	162
3. Y.P.	classic	8.5 yr	70	21	283	202
4. G.P.	classic	12.5 yr	91	15	349	120
5. T.G.	partial	10.5 yr	610	300	220	31

*Control values: HVA= 250-880; 5-HIAA=110-360

addition to the classical treatment. At the beginning of the trial neurotransmitter therapy was progressively reduced, and adjusted by clinical monitoring to obtain the maximal efficacy with the lowest precursor dose. Patients age at the onset of the trial ranged 5 months to 11.5 years, the interval between diagnosis and 1-Deprenyl administration ranged 4 months to 11 years and the duration of this medication ranged 7 months to 4 years (Table 2).

Results and Discussion

1-Deprenyl is a monoamine oxidase B-type inhibitor, relatively devoid of pressor effect in man (6), which is currently under evaluation in the treatment of Parkinson's disease (7,8). The scientific rationale of this therapy in BH_4 deficiency arises from its ability to increase the concentration of dopamine and serotonin in the brain by limiting the degradation of both neurotransmitters (9). Additional effects of potential advantage have been demonstrated. 1-Deprenyl can be metabolized to amphetamines, which enhance the re-uptake of dopamine, with antidepressant and anticholinergic effects (10). It also promotes the accumulation of phenylethylamine, which potentiates the action of dopamine (11), and displays a protective activity against different neurotoxins (12, 13).

The preliminary results here reported stongly indicate the beneficial effect of 1-Deprenyl in PTPS deficiency, as its administration allowed :

a) to treat a patient otherwise unresponsive to neurotransmitter therapy,

b) to relieve symptoms residual to neurotransmitter therapy in three patients

c) to reduce by 20 to 40% the previous dosage of neurotransmitter precursors;

d) to reduce in a patient the number of daily administrations of neurotransmitter precursors;

e) to stabilize the clinical response, avoiding the appearance of erratic symptoms of biogenic amine deficiency, or on-off phenomena.

As for the patient affected by partial PTPS deficiency, 1-Deprenyl therapy was tentatively introduced with the aim of correcting the progressive amine deficiency without neurotransmitter precursor administration. At present, however, as the patient is permanently asymptomatic it is not possible to evaluate possible benefits on a clinical basis.

No adverse effect, such as cardiac arrhythmia (14) or increased serum aspartate and alanine aminotransferase levels (15, 16), was observed with the dosage of 1-Deprenyl employed in our trial.Long term treatment will clarify whether the effect of 1-Deprenyl is merely symptonatic, as suggested by our preliminary results, or whether other mechanism(s) contribute to improve the outcome and prognosis of patients suffering from BH_4 deficiency.

Table 2. Treatment with 1-Deprenyl in five PTPS deficient patients

Patients	Age at onset of 1-Deprenyl therapy	Treatment before and after 1-Deprenyl adminstration mg/kg per day (daily administrations)				Cinical picture
		1-Deprenyl	BH_4	1-Dopa	5OH-Trp	
1. M.T.	5 mo	=	5.5(1)	5.2(3)	5.9(3)	unresponsive, myoclonic convulsions
		0.25	6.6(1)	3.6(3)	4.8(3)	=
2. I.A.	7 yr	=	8(1)	12(8)	9(8)	on-off phenomena, dystonia
		0.25	8(1)	8(3)	5(3)	=
3. Y.P.	7.5 yr	=	5(1)	6.3(3)	5.4(3)	end of dose symptons, diurnal clinical fluctuations
		0.25	5(1)	5(3)	4(3)	=
4. G.M.	11.5 yr	=	4.5(1)	6(3)	5(3)	wearing off symptons, depression
		0.25	4.5(1)	4.1(3)	3(3)	=
5. T.G.	10 yr	=	=	=	=	symptom free
		0.25	=	=	=	

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