

Short Communication

Deprenyl in the treatment of patients with tetrahydrobiopterin deficiencies

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Most patients suffering from tetrahydrobiopterin (BH₄) deficiency show an inadequate clinical outcome. Besides the administration of synthetic BH₄ or phenylalanine-restricted diet, neurotransmitter substitution with L-Dopa plus carbidopa (10:1) and 5-hydroxytryptophan is required. Motor and cognitive performances fluctuate apparently at random, especially when higher doses are required. To improve the clinical outcome and to avoid the late side-effects of the traditional L-Dopa treatment, an additional selective monoamine oxidase (MAO) B inhibitor, Deprenyl (selegiline), was introduced (Schuler et al 1995). Here we report on the clinical outcome of 8 patients with BH₄ deficiency, including our 7 years of experiences with additional deprenyl therapy.

METHODS AND PATIENTS

Blood phenylalanine (Phe) was measured by the Guthrie test. The diagnosis was obtained by a BH₄ loading test, the analysis of urinary pterins and the measurement of enzyme activity in red blood cells. CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) were measured before and during therapy (Blau 1996). Serum prolactin measurements were used recently as an indirect brain dopamine indicator. DQ was measured every 3 months under the age of 3 years and the IQ yearly above this age (Table 1). MRI, EEG, brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) were checked within the last 2 months.

All eight patients (Table 1) were suffering from 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency (McKusick 261640). There is consanguinity in two Gipsy

Table 1 Clinical data, treatment and IQ values of patients with 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency

	Present age	PTPS activity (% of controls)	Age at diagnosis	Age at initial treatment for PTPS	Age at starting Deprenyl	Treatment (mg/kg per day)				DQ/IQ ^a
						BH ₄	5-Hydroxy tryptophan	(+ 10% L-Dopa + carbidopa)	Deprenyl	
M.R.	1.5 y	1.3	Newborn screening	1 wk	1 wk	3.30	4.20	4.20	0.240	94
A.Z.	8 y	2.4	7 y	7 y	7 y	3.30	3.30	2.08	0.250	43
G.T. ^b	8 y	13.6	Newborn screening	2 wk	6 y	3.30	3.54	2.30	0.180	91
T.M.	8 y	0	Newborn screening	2 wk	5 mo	2.08	7.80	3.90	0.250	81
L.A.	8 y	7	5 mo	6 mo	7 y	2.78	7.50	8.33	0.250	74
T.I.	14 y	5.9	6 y	9 y	9 y	2.71	3.50	—	0.088	100
T.A.	20 y	7.2	12 y	—	—	—	—	—	—	100
P.Á	16 y	8	Newborn screening	7 mo	15 y	1.7	1.70	7.22	0.22	43

^a DQ: 0–3 years, Brunet–Lézin test. IQ: 3–14 years, Budapest–Binet; > 14 years, MAWI, HAWIK

^b Treated until the age of 6 years treated by Dr Janina Soltysiak (Szeged Screening Center): + pyridoxine 1 mg/kg per day; + calcium folinate 0.6 mg/kg per day (because of the low level of 5-methyltetrahydrofolate in CSF)

families (M.R./A.Z. and L.A.). One patient (the brother of L.A.) died suddenly at the age of 5 months during an intercurrent infection (bacterial pneumonia). Patient G.T. presented with an oculogyric crisis. The mentally retarded and hypotonic A.Z. was found by family screening at the age of 7 years with a blood Phe level of 180 $\mu\text{mol/L}$ after the diagnosis of his newborn brother. Six months after starting the therapy, muscle tone and mood improved. T.I. and his sister T.A. were initially treated as milder forms of classical PKU. They were put on a diet until T.I. presented with clinical symptoms with vertigo, balance disturbances and timidity. A BH_4 loading test was performed in both of the children, which confirmed a PTPS deficiency. Since his sister, T.A., showed no clinical symptoms, she is not being treated.

Two of eight patients were treated traditionally and in four patients the additional Deprenyl therapy was used at a dose of 0.088–0.25 mg/kg per day (Table 1). In all of the patients the daily doses were divided into 3–4 portions.

RESULTS AND DISCUSSION

During the past 25 years of newborn screening at the Budapest screening centre, 188 patients with PKU were found in 1 633 529 blood samples. The incidence for classical PKU was found to be 1 : 9000 (180 patients) and for BH_4 deficiencies 1 : 200 000 (8 patients).

The DQ/IQ levels for half of the patients were within the normal range, while two patients measured 74 (L.A.) and 81 (T.M.). Of the two patients whose IQs were 43, A.Z. was diagnosed at the age of 7 years through family screening and P.A.'s treatment was inadequate because of a lack of collaboration on the part of the parents.

The seven neurophysiological examinations showed prolonged I-V interpeak latency in the BAEP in two patients (G.T., L.A.) and prolonged visual evoked potentials (VEP) in two patients (A.Z., L.A.). Mild demyelination was found in the MRI of two brothers (M.R., A.Z.) out of eight patients. Paroxysmal signs were seen in the EEG of one patient (M.R.) during spontaneous sleep. Interestingly, in four patients (T.M., T.A., T.I., L.A.), including the 19-year-old symptom-free girl (T.A.), photosensitivity was found in the EEG.

As a result of the additional Deprenyl therapy, the dosage of L-Dopa was reduced to about 40% and in some cases the 5-hydroxytryptophan was also reduced. The clinical status of the patients improved significantly: convulsions disappeared (T.M.); the on-off phenomenon, caused by L-Dopa administration, was avoided; behaviour and achievements improved. The patient with a 1.3% residual PTPS activity receiving Deprenyl from his first week of life (M.R.) showed excellent motor and brain development.

The presented and the previously reported cases of PTPS (Spada et al 1995) and dihydropteridine reductase (DHPR: EC 1.6.99.10) deficiencies (Spada et al 1996) give hope that optimal results and, as already seen in patients with parkinsonism, beneficial long-term effects can be achieved by the addition of the selective MAO-B inhibitor, Deprenyl (Knoll 1998), to the classical treatment.

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