J. Inher. Metab. Dis. 19 (1996) 231–233

Short Communication – SSIEM Award

Monitoring treatment in tetrahydrobiopterin deficiency by serum prolactin

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Hyperphenylalaninaemia, dopamine and serotonin deficiencies are the main metabolic disturbances caused by tetrahydrobiopterin (BH_4) deficiency, irrespective of the enzyme defect leading to impaired cofactor synthesis or regeneration. While hyperphenylalaninaemia can be easily controlled by dietary or synthetic cofactor treatment, it is often hard to ensure neurotransmitter homeostasis at the central level by administering the hydroxylated precursors. Major concerns are with their optimal dosages, as neither biochemical measurement of CSF neurotransmitter metabolites nor clinical monitoring are adequately informative (Ponzone et al 1990; Spada et al 1992).

Since dopamine is the essential inhibitory factor of prolactin (PRL) secretion, we evaluated serum PRL levels in seven BH_4-deficient patients before and while on therapy as a simple tool for treatment monitoring.

PATIENTS AND METHODS

Three patients suffering from 6-pyruvoyltetrahydropterin synthase (PTPS; McKusick 261640) deficiency, and four suffering from dihydropteridine reductase (DHPR; McKusick 261630) deficiency, aged 7 to 13 years, were evaluated at diagnosis and during therapy for serum PRL concentration and CSF neurotransmitter metabolites homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA). Blood and CSF samples were obtained 1–2 h after awakening. Serum PRL was measured by a standard immunoradiometric assay and CSF HVA and 5-HIAA by HPLC with an ESA Coulochem 5100 A electrochemical detector.

After diagnosis, all PTPS-deficient patients had a classical treatment with synthetic BH_4, L-dopa, 5-hydroxytryptophan, plus carbidopa. Three DHPR-deficient patients were treated with phenylalanine-restricted diet, folinic acid and neurotransmitter substitutive therapy, and one had BH_4 monotherapy. Recently, all patients were begun on an innovative therapeutic approach with a monoamine oxidase inhibitor, L-deprenyl, at the dose of

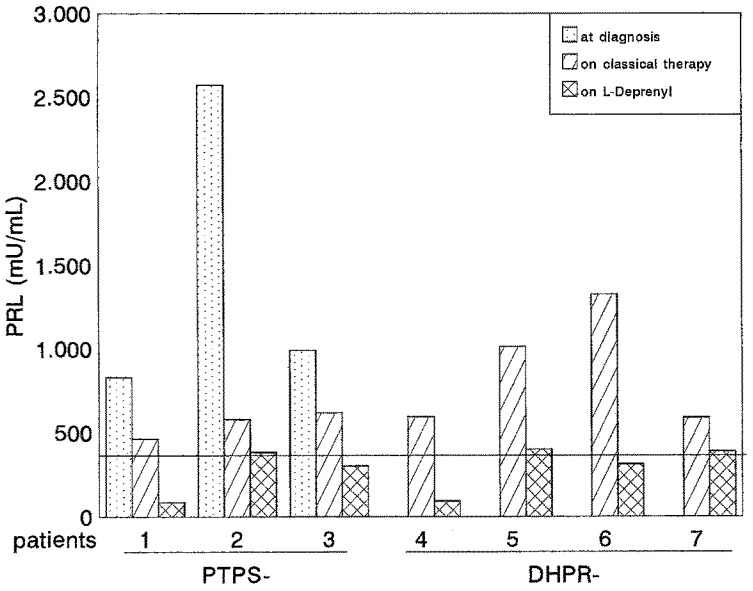

Figure 1 Serum prolactin (PRL) concentrations and treatment in 3 patients affected by 6-pyruvoyl-tetrahydropterin synthase deficiency (1–3, PTPS-) and in 4 patients affected by dihydropteridine reductase deficiency (4–7, DHPR-)

0.25 mg/kg per day, allowing for concomitant reduction of neurotransmitter precursors (Schuler et al 1995).

RESULTS AND DISCUSSION

Outcome of patients affected by inherited BH_4 deficiency is often poor despite early treatment. Many failures are consequent on difficulties in managing the neurotransmitter substitutive therapy, mostly because of dopamine fluctuations (Tanaka et al 1989). Actually, clinical monitoring of this treatment is hampered by the composite picture resulting from agonist, antagonist, and side-effects of L-dopa and 5-hydroxytryptophan, which can also mimic the symptoms of deficiency. Direct biochemical monitoring, on the other hand, is restrained by the lack of a good correlation between neurotransmitter concentration in CSF and clinical symptoms (Spada et al 1992).

The potential of an indirect monitoring of treatment by the evaluation of PRL secretion in BH_4 deficiency was evaluated in the present study. Dopamine originating from the hypothalamic tuberoinfundibular tract is the major physiological PRL inhibitor factor. PRL secretion displays marked variations during the day, but is not controlled by a circadian rhythm: a constant hormone rise is observed after the onset of sleep, with a gradual decline throughout the night, and lowest levels are found shortly after awakening. Thus, this time is generally chosen for the basal evaluation of PRL secretion. Basal serum PRL levels are physiologically very low during childhood, remaining below the upper value of 300 mU/ml.

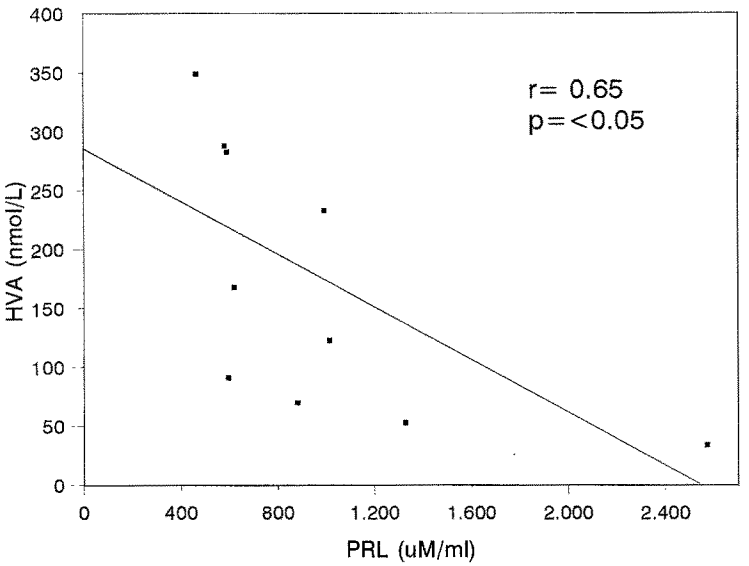

Figure 2 Correlation between CSF homovanillic acid (HVA) and serum prolactin (PRL) concentrations in 7 patients with tetrahydrobiopterin deficiency

As expected, impaired dopamine synthesis resulted in moderate to high hyperprolactinaemia (830–2573 mU/ml) in all PTPS-deficient patients at the time of diagnosis and before treatment (Figure 1). On classical treatment (diet or synthetic cofactor, neurotransmitter therapy), serum PRL levels decreased (465–620 mU/ml) in PTPS-deficient patients; in DHPR-deficient patients, whose pretreatment levels had not been determined, serum PRL concentrations ranged from 590 to 327 mU/ml (Figure 1). With the addition to this treatment of L-deprenyl, PRL levels dropped into the normal range (85–401 mU/ml) in both PTPS- and DHPR-deficient patients (Figure 1).

Serum PRL and CSF HVA concentrations were inversely related (Figure 2). Obviously, this relation could not be tested on L-deprenyl therapy because of its limiting effect on dopamine degradation. At the clinical level, optimal results were obtained after L-deprenyl was added to the classical therapy, and normalization of PRL secretion paralleled the disappearance of residual or fluctuating symptoms.

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