A New Case of Dihydropyrimidine Dehydrogenase Deficiency

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Summary: We present the clinical and biochemical features of a boy with
dihydropyrimidine dehydrogenase deficiency, which seem to underline a disease
entity of developmental retardation, epilepsy and muscular hypertonia.

Dihydropyrimidine dehydrogenase (DHPDH) deficiency (EC 1.3.1.2) was first postu-
lated as an inborn error of pyrimidine metabolism, McKusick 27427, by van Gennip
et al. (1981a) in a 4-year-old boy with transient seizures, speech retardation and
behavioural problems. The deficiency of the enzyme was confirmed by Berger et
al. (1984). An elevated excretion of thymine and uracil, as seen on gas–liquid
chromatography of the patient's urine, is the biochemical marker indicating a
deficiency of the thymine- and uracil-degrading enzyme DHPDH, which can be
measured in leukocytes (Goedde et al., 1968; Piper et al., 1980), fibroblasts (Bakkeren
et al., 1984) or liver (Shiotani and Weber, 1981).

Hitherto eight paediatric patients have been described (van Gennip et al., 1981a;
Bakkeren et al., 1984; Berger et al., 1984; Wadman et al., 1985; Wilcken et al., 1985;
ván Gennip et al., 1987a), from which seven are of Dutch origin. The clinical features
often comprise a convulsive disorder as well as hypertonicity and/or microcephaly.
Some patients are mentally retarded. Minor dysmorphic features such as hypertelor-
ism, broad nose and lacunar teeth have been noted, and in one instance hypohydrotic
ectodermal dysplasia and hepatosplenomegaly.

The first patient described has developed unremarkably; he shows only a mild
behavioural disorder. Recently a 40-year-old female patient has been described, who
showed signs of severe 5-fluorouracil-induced toxicity during treatment for breast
cancer and who previously had been completely healthy (Diasio et al., 1988). The
variable clinical presentation of the patients so far diagnosed raises the question
whether or not the biochemical abnormalities really present a disease entity with
heterogenous expression or simply a genetic trait. We want to add information about
a further patient, which might help to elucidate this question.

MS received 27.4.89 Accepted 12.7.89
CASE REPORT

The patient is the second son of healthy non-consanguineous Dutch parents. The father has a mild asymptomatic microcephaly (head circumference 52 cm). The mother and the patient's 3-year-old brother show no abnormalities. The boy was born spontaneously at term after an uneventful pregnancy; birthweight was 3500 g, length 51 cm, head circumference 37 cm. After 3 months he suffered recurrent upper respiratory tract infections. After the age of 6 months his parents noted delay in psychomotor development. At the age of 13 months a febrile viral infection provoked a generalized convulsion and the boy was admitted to our hospital. Clinical examination revealed a microcephalic (43.5 cm) boy with normal weight and length. The extremities were rather thick but not oedematous. There was evident psychomotor retardation. The boy had a mild generalized hypertonia and an axial imbalance. He could not sit in an upright position without support. He showed short-lasting visual fixation, inadequate explorative behaviour and no use of comprehensive language. Ophthalmological examination revealed megalocorneae, hypopigmentation of the fundus and pallor of optic discs.

Neurophysiological and neuroradiological examinations revealed a pathological EEG with focal paroxysms of sharp waves in the temporo-occipital region, with a generalized slowing of background activity. Visual and brainstem auditory evoked potentials were within normal limits. CT scan revealed fine symmetric calcifications in the basal ganglia and a megacisterna magna. Nuclear magnetic resonance imaging (NMR) of the brain showed a tiny corpus callosum and a prominent retardation of myelination. Between the frontal parts of the lateral ventricles a distortion of the parenchymal architecture was seen, pushing the anterior cerebral arteries laterally. This lesion gave the impression of a hamartoid malformation, without evident space-occupying character. Repeated NMR investigation at 22 months of age showed only a slight progression in myelination.

Biochemical examination of the patient's urine by gas chromatography–mass spectrometry (GC–MS) showed a thymine-uraciluria (see Table 1) with otherwise normal organic acid concentrations. In addition, an elevated excretion of 5-hydroxymethyluracil was established by high pressure liquid chromatography (HPLC). Plasma and urinary amino acids, plasma ammonia, lactate and pyruvate, urinary excretion of catecholamines as well as routine clinical biochemistry were normal. The enzyme defect was confirmed in leukocytes of the patient (DHPDH activity 0.003 nmol h⁻¹ (mg protein)⁻¹ versus 0.38 nmol h⁻¹ (mg protein)⁻¹ in controls).

Table 1 Excretion (μmol/g creatinine) of thymine, 5-hydroxymethyluracil and uracil in the index patient, his parents and controls

<table>
<thead>
<tr>
<th></th>
<th>Thymine</th>
<th>5-Hydroxymethyluracil</th>
<th>Uracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>4140</td>
<td>575</td>
<td>5525</td>
</tr>
<tr>
<td></td>
<td>3034</td>
<td></td>
<td>4386</td>
</tr>
<tr>
<td>Father</td>
<td>4</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>Mother</td>
<td>3</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>Controls (n = 6)</td>
<td>7</td>
<td>n.d.</td>
<td>70–300</td>
</tr>
</tbody>
</table>

n.d. = not detected

J. Inher. Metab. Dis. 13 (1990)