Short reports

Basal ganglion calcification in hyperphenylalaninemia due to deficiency of dihydropteridine reductase

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Abstract. The disease course and therapy of a nine-and-a-half-year-old boy with hyperphenylalaninemia due to a dihydropteridine reductase deficiency are reported. Clinically, there is a marked mental retardation and complex basal ganglion symptoms. The cranial computed tomographic investigation shows bilateral, symmetrical, comma-shaped calcifications in the globus pallidus and the putamen of the lentiform nucleus. The cause of these basal ganglion calcifications remains unclear. Lowering of serum and CSF folic acid levels could not be detected, in contrast to cases with the same enzyme defect described previously.

The enzyme dihydropteridine reductase converts quinoid dihydropteridine into tetrahydrobiopterin (BH₄), the cofactor of phenylalanine, tyrosine and tryptophan hydroxylase. Patients with dihydropteridine reductase deficiency do not only display hyperphenylalaninemia, but also a deficiency of neurotransmitters such as 3,4-dihydroxyphenylalanine (Dopa) and 5-hydroxytryptophan [1-4]. The patients are not only treated dietetically, but also with substitution therapy with administration of the neurotransmitters Dopa, 5-hydroxytryptophan and a decarboxylase inhibitor (Carbi-Dopa®), which prevents decarboxylation of Dopa and 5-hydroxytryptophan outside the CNS [5-7] in order to avoid the neurological symptoms.

In the present study, the disease course and therapy of a nine-and-a-half-year-old boy patient with dihydropteridine reductase deficiency will be presented and the possible causes of the basal ganglion calcifications shown by computed tomography will be discussed.

Description of the patient

The clinical development up to the 18th month of life as well as the biochemical characterization of the enzyme defect have been described in a previous publication [8]. From the age of about two-and-a-half years, a retarded motor and mental development with a delayed development of speech were noticed. Athetoid movements of the hand as well as enhanced monosynaptic reflexes which were the same on both sides were described for the first time at the age of three years. At the age of seven years, there was metabolic dysregulation with loss of consciousness, a hint of menigism, tetrapsynticity, enhanced monosynaptic reflexes, ankle cloni and hypersalivation in the context of a febrile infection with enteritis. After increased neurotransmitter intake, the clinical picture regressed within two days. Now (at the age of nine-and-a-half years), fearfulness, motor unrest, athetoid arm movements, broad gait and enhanced monosynaptic reflexes identical on both sides are noticeable in the boy besides his motor and mental retardation. The motor development of the nine-and-a-half-year-old corresponds to that of a six-year-old child.

The following test results were determined: CMM-LB (Columbia Mental Maturity Scale for the learning handicapped): T value of 30 (normal range: T value of 40-60). Hawiva test (Hannover-Wechsler intelligence test for pre-school age): Activity IQ of 70, verbal IQ of 50. An LOS test (Lincoln Oseretzky Scale) could not be carried out.

Between the first and fourth month of life, there was a decrease of cranial circumference from the region of the 25th to the region of the 3rd percentile. The further development of cranial circumference paralleled the third percentile. The curve of growth in length was normal. Cerebral convulsions were not observed. Repeated electroencephalograms (EEG) did not display any attack-specific potentials. Visual evoked and acoustic evoked potentials are normal at the age of 9.5 years and there is thus no indication of a disturbance of conduction in the region of the brainstem as well as in the region of the optic radiation.

A low-phenylalanine diet was started in the third week of life. This was switched to a protein-reduced diet from the sixth month of life. The serum phenylalanine values determined under this therapy were between 0.8 and 13.9 mg/dl (average value 4.6 mg/dl, n = 60). After diagnosis in the sixth month of life, a neurotransmitter therapy with Dopa and 5-hydroxytryptophan as well as Carbi-Dopa® was commenced with an average dosage of 11.0, 10.0 and 0.8 mg/kg body weight/day respectively (ranges: 6.1 to 15.8, 3.9 to 14.2 and 0.5 to 1.2 mg/kg body weight/day respectively). After reduction of the tryptophan dose from 12 to 8 mg/
kg body weight/day at the age of 9 years, there was a certain decrease of motor unrest as well as of the athetoid movements. Administration of BH₄ at a dosage up to 10 mg/kg body weight did not lead to any lowering of the serum phenylalanine levels at the ages of 3.5 and 9 years, so BH₄ therapy was dispensed with for this reason.

Results

Biochemical findings

Both the serum and CSF levels of folic acid and the CSF concentrations of homovanillic acid and 5-hydroxyindoleacetic acid as well as the serum concentrations of vitamin B₁₂, lactate, pyruvate and total carnitine were in the normal range [9, 10]. The CSF concentrations of total biopterin were 64.1 to 76.3 nmol/l (Table 1).

Radiological findings and Discussion

The CT showed bilateral symmetrical, comma shaped calcifications in the globus pallidus and putamen of the lentiform nucleus. There were no signs of leukodystrophy. The external and internal CSF system was symmetrical and of normal width (Fig. 1).

In contrast to the present case, there were not only calcifications in the basal ganglia in the cases described by Smith et al. and Tarda et al., but also in the white and grey matter. Furthermore, multiple macular alterations of the white matter were observed, which were regarded to be a result of a demyelination process. Lowered serum and CSF folic acid levels could be demonstrated in these patients, which were regarded as the cause of the described calcifications analogous to those in congenital folate malabsorption syndrome [1]. In contrast to these patients [15, 16], the serum and CSF folic acid levels of our patient were in the normal range. There were no dorsal column symptoms and both the CCT and the evoked potentials did not show any indication of the presence of a demyelination process. Basal ganglion calcifications have also been described after methotrexate and radiotherapy [17, 18]. By inhibition of dihydrofolate reductase, methotrexate treatment leads to a lowered formation of tetrahydrofolic acid. The concentration of total biopterin in the CSF is raised in dihydropterdine reductase deficiency (Table 1). To what extent this substrate accumulation leads to a lowering of reduced folic acid derivatives by inactivation and saturation of other enzyme systems with consequently reduced synthesis of purine bodies and neurotransmitters is unclear [1, 15, 19, 20]. In some cases, therapy with folic acid, if begun early in infancy, leads to an improvement of neurological symptoms [20]. In comparison to the cases described in the literature, this patient has received a relatively high dose of 5-hydroxytryptophan. Nevertheless, the CSF levels of hydroxyindoleacetic acid were in the normal range [2, 10]. After reduction of the 5-hydroxytryptophan dose at the age of nine years, there was a certain reduction of the athetoid movement and the restlessness of the patient, so that some of the symptoms are to be regarded as a result of the neurotransmitter therapy. Restlessness and dyskinesia are described both as a result of 5-hydroxytryptophan and of Dopa overdosage [2, 11–13].

On the other hand, the hyperactivity of patients with classic phenylketonuria has been regarded as a consequence of serotonin deficiency [12]. Birmeyer et al. [21] describe a progressive neuronal degeneration owing to an intensified presynaptic and postsynaptic imbalance in Parkinson’s disease due to

| Table 1. Concentrations of folate , homovanillic acid (HVA) ++, 5-hydroxyindoleacetic acid (5-HIAA) ++ and total biopterin (BT) ++ |
|---|---|---|---|---|
| Age (years) | 8.0 | 9.0 | 9.5 | Normal values |
| Serum folate (ng·ml⁻¹) | 3.9 | 5.2 | 3.0–17.0 | + |
| CSF folate (ng·ml⁻¹) | 15.1 | 13.0–38.0 | + |
| CSF HVA (nmol·l⁻¹) | 272 | 318 | 250–880 | + |
| CSF 5-HIAA (nmol·l⁻¹) | 286 | 251 | 110–360 | + |
| CSF BT (nmol·l⁻¹) | 76.3 | 64.1 | 10–24 | + |

† Total folate (Lactobacillus casei assay, Bioscientia, Institut für Laboruntersuchungen, Ingelheim)  
++ Measurements of metabolites in cerebrospinal fluid (CSF) were carried out by Prof. Dr. A. Niederwieser, Kinderspital Zürich

Fig. 1. Nine-and-a-half-year-old boy with hyperphenylalaninemia due to a dihydropterine reductase deficiency and bilateral, symmetrical, comma-shaped calcifications in the globus pallidus and the putamen of the lentiform nucleus.