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INTRACRANIAL CALCIFICATION IN DIHYDROPTERIDINE REDUCTASE DEFICIENCY*

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We described the clinical status and computerized tomographic findings of two patients with tetrahydrobiopterin (BH_4) deficiency due to impaired BH_4 regeneration. In addition to an unfavorable course, cranial computerized tomography scans demonstrated severe cortical and subcortical atrophy and bilateral corticomedullary and basal ganglia calcifications in these two cases. The occurrence of calcification in the same distribution following the use of methotrexate, a folic acid antagonist, supported the hypothesis that there is a link between the metabolism of pterins and folate. *Key words: dihydropteridine, reductase deficiency, hyperphenylalaninemia, intracranial calcification.*

Tetrahydrobiopterin (BH_4) is a specific cofactor for phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp) hydroxylases. The deficiency, therefore, of this cofactor results in hyperphenylalaninemia associated with low levels of the monoamine neurotransmitters dopamine, norepinephrine and serotonin. BH_4 deficiency may be either due to a defect in regeneration of BH_4 from quinonoid dihydrobiopterin (qBH4) or in its biosynthesis. Dihydropteridine reductase (DHPR) catalyses the regeneration reaction of BH_4, whereas 6-pyruvoyl tetrahydropterin synthase (PTPS) and GTP-cyclohydrolase have a role in BH_4 biosynthesis. The clinical picture of hyperphenylalaninemias due to BH_4 defects differs from that of other hyperphenylalaninemias, in that they show a progressive neurological deterioration despite early and adequate dietary therapy[1].

In this report, we describe the cerebral computed tomographic (CT) findings of two patients with DHPR deficiency of which very few cases have been reported in the literature[2-6]. Our results draw attention to the association of this type of hyperphenylalaninemia with intracranial calcification.

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Case Reports

Case 1

Patient E.K., a five-year-old girl, was born weighing 3100 g. Pregnancy, labor and delivery had been uncomplicated. The parents were unrelated. Her blood samples were screened for hyperphenylalaninemia because her elder sister had been diagnosed as having hyperphenylalaninemia due to DHPR deficiency. Her blood Phe level rose gradually and reached 15 mg/dl by the seventh day of life. Subsequent urinary pterin analysis and measurement of DHPR activity in the erythrocytes confirmed the diagnosis of DHPR deficiency. On the eighth day of life, a restricted Phe diet was initiated. L-Dopa/Carbidopa and 5-OH-tryptophan were instituted as neurotransmitter precursors. Her blood Phe level was well under control. Her psychomotor development was normal until seven months of age, when she first experienced a convulsive attack. Myoclonic seizures continued to occur despite the combined anticonvulsive therapy administered. There was also evidence of progressive neurological deterioration. The first CT brain scan, taken at two years of age, demonstrated the presence of cortical atrophy of the brain and multiple foci of calcification at the level of the basal ganglia. Folinic acid was added to the therapeutic regimen but no clinical improvement was evidenced. A repeat CT scan, at five years, revealed dilatation of the hemispheric cortical sulci, ventricles and cisterns due to severe cortical and subcortical atrophy. Bilateral, symmetric cortico-medullary junction and basal ganglia calcifications were also observed (Fig. 1 a, b).

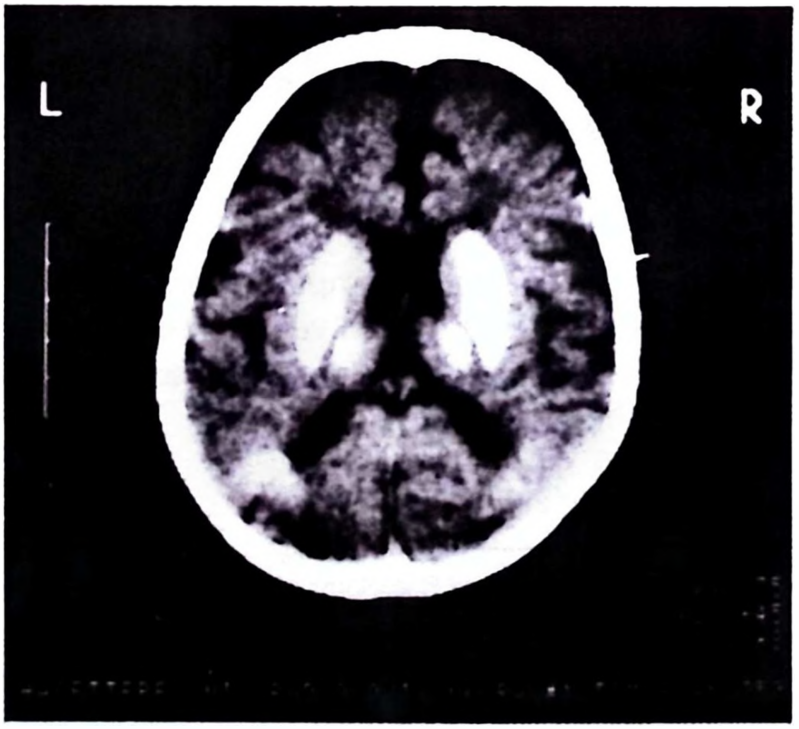
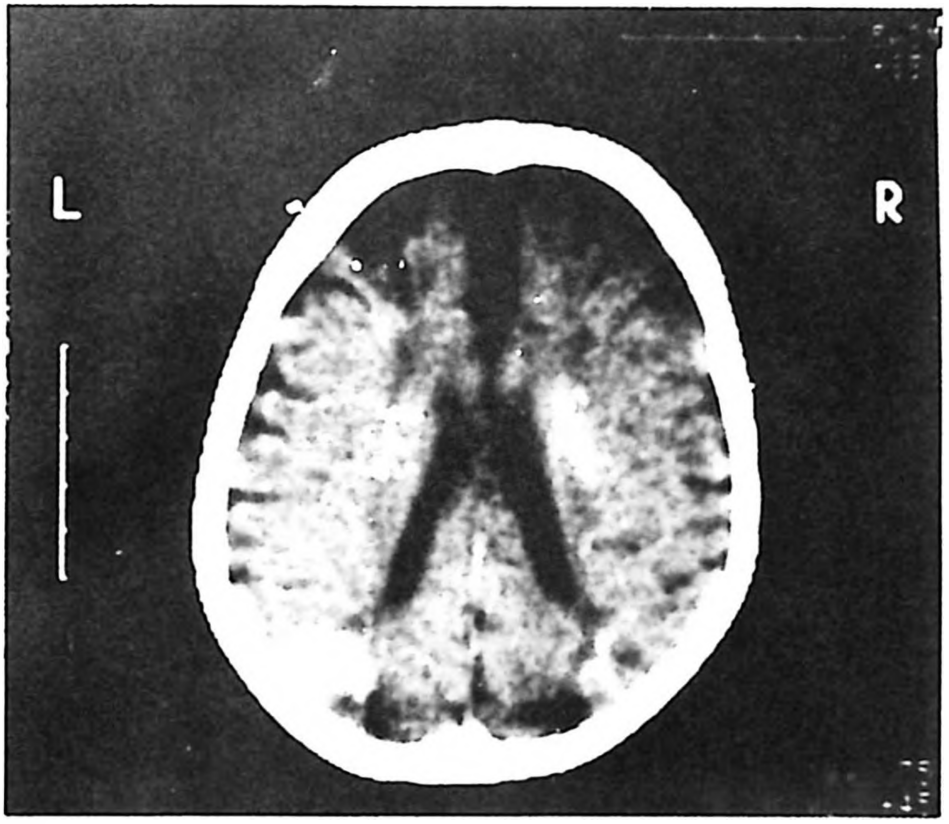


Fig. 1 a, b: The CT images, which are not enhanced, show bilateral symmetric calcification of lentiform and thalamic nuclei and of the cortico-medullary junction in the parieto-occipital lobes (Case 1).

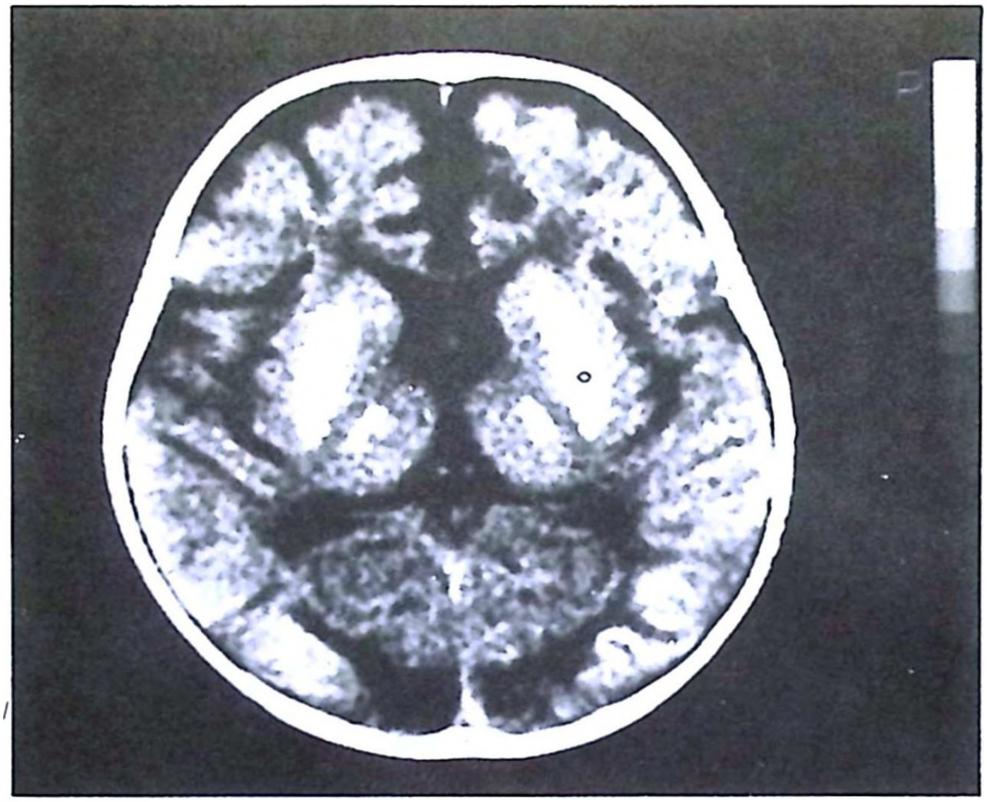


b

Case 2

Patient B.Y., a 13-month-old girl, was brought to Hacettepe University Children's Hospital with the chief complaints of developmental delay and spasticity. Pregnancy and delivery were both uneventful. The parents were first cousins. The first born child, a 1.5-year-old girl, had died demonstrating the same clinical signs and symptoms.

Physical examination revealed that the patient was below the 5th percentile for weight (5700 g) and at the 5th percentile for height (70 cm). Her head circumference of 41 cm was below the 5th percentile. She was unable to recognize her mother, sit unaided, and was not interested in her surroundings. Her extremities were extremely spastic and there was truncal hypotonia. Laboratory investigations revealed that the blood Phe level was 13.8 mg/dl. The results obtained from urinary pterin analysis and from measuring DHPR activity were consistent with the diagnosis of DHPR deficiency. A CT brain scan demonstrated the same features as Case 1 (Fig. 1 c, d). The patient was given a low Phe diet and the neurotransmitter precursors L-Dopa and 5-OH-tryptophan shortly after confirmation of the diagnosis.



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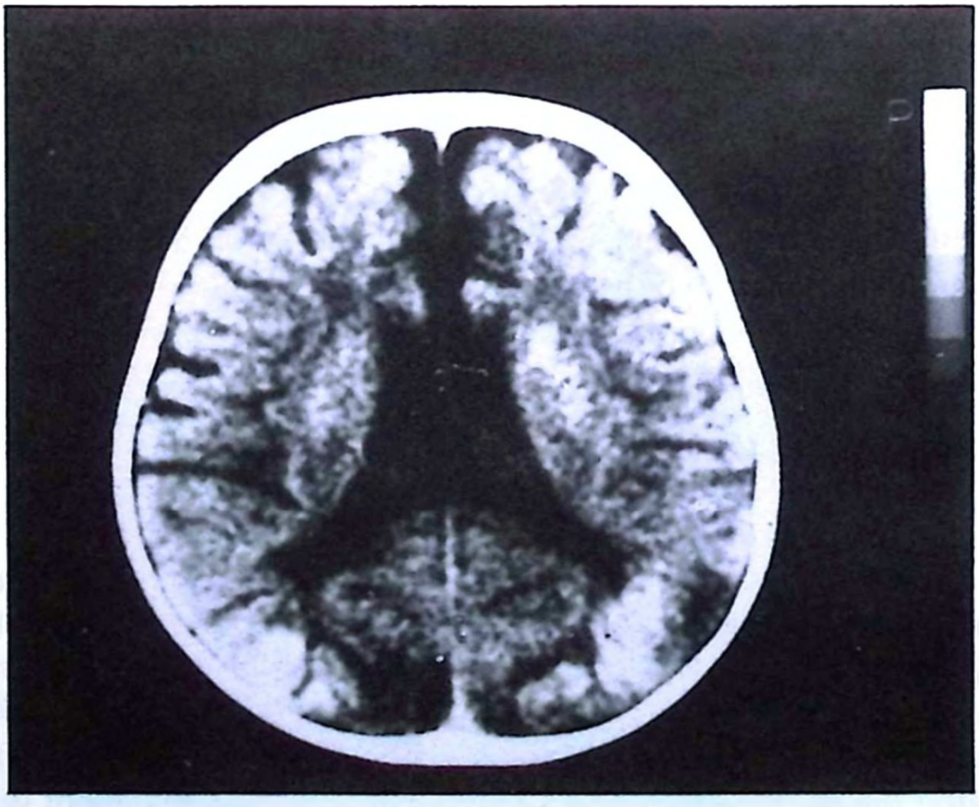

d

Fig. 1 (c, d): The ventricles and hemispheric cortical sulci are dilated because of cortical and subcortical atrophy (Case 2).

Discussion

Deficiency of DHPR, an enzyme involved in the regeneration of the cofactor BH_4, is one of the three inborn errors of metabolism causing BH_4 deficiency. Since BH_4 is a cofactor not only of phenylalanine hydroxylase, but also of Tyr and Trp hydroxylase, an atypical form of phenylketonuria (PKU) with progressive neurological symptoms which are unresponsive to a Phe restricted diet, develops when there is a defect either in BH_4 regeneration or in its biosynthesis[1].

Neuroradiological studies in children with classical PKU have demonstrated only cerebral atrophy, probably due to demyelinization[7]. In CT scans of our two patients with DHPR deficiency, there were intracranial calcifications at the cortico-medullary junction and the basal ganglia, in addition to cerebral atrophy. Basal ganglia calcification occurs under a wide range of conditions[4]. The number of recognizable metabolic derangements described in association with basal ganglia calcification has increased in recent years with the availability of computed tomography. In our cases, an abnormality in calcium metabolism was excluded by routine biochemical tests. Few previous reports have noted the presence of intracranial calcifications in DHPR deficiency[2-6]. The mechanism responsible for intracerebral calcification in DHPR-deficient patients has not yet been fully clarified. In addition to the cases which have been previously reported,our two cases add further support to the hypothesis that the presence of intracerebral calcification in DHPR deficiency is not a coincidental finding.

In fact, there have been reports of cases ascribing the development of intracerebral calcifications in DHPR deficiency to folate deficiency in the central nervous system (CNS) resulting from the loss of the folate conservative effect of DHPR in CNS[3,5]. In addition, the pattern of calcification and atrophy seen in our cases is exactly the same as that observed in cases of mineralizing microangiopathy which occurs in children treated with cranial irradiation and methotrexate, a folic acid antagonist[8].

In conclusion, we believe that the presence of intracerebral calcifications in DHPR-deficient children is not just a mere coincidence but points to a common mechanism. We, therefore, propose that DHPR deficiency should be included in the list of causes of intracerebral calcifications visualized by CT scans in children. Awareness of this possibility will lead to performance of necessary laboratory investigations in a child with hyperphenylalaninemia characterized by progressive neurological deterioration which is unresponsive to dietary therapy alone.

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