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Malignant Hyperphenylalaninemia: CT and MR of the Brain

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A defect in the bipterin synthesis not only prevents the transformation of phenylalanine to tyrosine (as in classical phenylketonuria, PKU) but also blocks the biosynthesis of the neurotransmitters dopamine, norepinephrine, and serotonin, causing severe neurologic disturbances. The brain CT and MR findings in this rare disorder have not been described. In the present series, eight patients with PKU were all examined with CT, three were also examined with MR imaging. In spite of severe clinical findings, CT was normal or almost normal in three patients; in three other children, moderate loss of brain volume was found. White matter disease was found in three patients (moderate in two and severe in one) and was also found in an additional patient with classical PKU. PKU should therefore be added to the list of possible causes for white matter disease. Furthermore, bipterin-dependent PKU should be considered when the CT examination in a child with severe neurologic manifestation only shows discrete pathology.

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Phenylketonuria (PKU), present in approximately 1/10,000 newborns, is caused by a metabolic block preventing the transformation of phenylalanine to tyrosine. The accumulation of phenylalanine in the brain causes severe mental retardation, a development that in classical PKU can be prevented by the early institution of a diet low in phenylalanine. In spite of an early and rigorous diet regimen, however, some 2% of children with PKU develop a severe and progressive neurologic disease [1], which in about one fifth of the patients has a fatal outcome [2]. The hyperphenylalaninemia (HPA) in these patients is not caused by a lack of the enzyme phenylalanine hydroxylase, as in classical PKU, but by a deficiency of a cofactor essential for the hydroxylation process. This cofactor (tetrahydrobiopterin, BH₄) is also a prerequisite for the conversion of tyrosine to L-dopa and of tryptophan to 5-hydroxytryptamine [3]; a cofactor deficiency, therefore, also impairs the biosynthesis of the neurotransmitters dopamine, norepinephrine, and serotonin, causing severe neurologic disturbances. BH₄ is synthesized from GTP (guanosine triphosphate) through a metabolic pathway involving, in order, the enzymes GTP-cyclohydrolase, pyruvoyltetrahydropterin synthase, and sepiapterin reductase. Metabolic blocks involving the first two of these enzymatic steps have been described in four and 60 cases, respectively [2]. Also, a deficiency in the enzyme DHPR (dihydropteridine reductase), which ensures a salvage of the active form of the cofactor, causes BH₄ deficiency (38 cases have been reported) [2].

We have during the last year identified eight patients with HPA caused by a lack of the enzyme pyruvoyltetrahydropterin synthase. These patients form the basis for this report.

Materials and Methods

The members of one of the tribes in Saudi Arabia have long known that their children run the risk of being affected by a lethal disease characterized by myoclonal seizures, truncal

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hypotonia, limb spasticity, and mental retardation. We have had the opportunity to examine eight children from this large tribe during the last two years. All patients at diagnosis had an elevated blood phenylalanine level. A provocation test in seven of the patients (not performed in case 6) proved the HPA to be BH₄-dependent. The blood phenylalanine level, after having been allowed to rise through free diet, immediately decreased after BH₄ administration and then increased again when BH₄ was discontinued. Furthermore, in all eight patients, high-pressure liquid chromatography showed increased neopterin and no biopterin in the urine, thereby suggesting the block to be in the second step in the BH₄ synthesis. In addition to an extensive biochemical workup and a thorough clinical/neurologic evaluation, all the children also had CT of the brain (GE 9800, 10-mm consecutive tomograms), and three also had brain MR (Picker 1.5 T, SE 2000/40,80, 7-mm consecutive slices). In three patients multiple CT examinations were performed, both before and after therapy. The detailed clinical and biochemical findings will be presented elsewhere; a summary of relevant data is given in Table 1. The CT examinations were specifically evaluated for ventricular dilatation, for prominence of sulci and fissures ("cortical atrophy"), and for white matter disease. The radiologic findings were subjectively graded as absent (N), slight (+), significant (++), or severe (+++).

Case Report

Case 2 was the product of a consanguineous marriage (parents were first cousins); delivery and the neonatal period were normal. She presented at age 2 months with myoclonic seizures. Physical examination was normal, CT of the brain showed slight prominence of the sulci (Fig. 1A). As her older brother (case 1) was a known case of PKU, serum phenylalanine was analyzed and found elevated (2.2 mol/100 ml). A low phenylalanine diet was started, and the phenylalanine level soon fell to normal and the clinical condition improved.

She presented again at age 6 months with myoclonic seizures, loss of visual pursuit, truncal hypotonia, and some lower leg spasticity. CT showed wider fissures and sulci (Fig. 1B).

At 13 months she had lost all her milestones (estimated developmental age 1–3 months) and was readmitted for evaluation. CT (Fig. 1C) showed further progress with significant widening of fissures and sulci and also slight ventricular enlargement. Soon after admission, after a mild febrile episode, she started to eat poorly, developed tachypnea, dyspnea, stridor with abundant secretion, generalized tonic-clonic seizures, and stupor. Her condition deteriorated rapidly,

and she became obtunded and severely dyspneic. She was therefore treated as biopterin-dependent PKU with 50 mg L-5-hydroxytryptophan, 100 mg L-dopa, and 10 mg carbidopa orally before the test results arrived. Within 2 hr she improved suddenly and miraculously. She opened her eyes, became responsive, started to follow with her eyes, and smiled; the dyspnea and tachypnea disappeared. Urine pterins and BH₄ provocation tests confirmed biopterin-dependent PKU. She has now been on medication for 1 year, is free from symptoms and signs, and has recovered much of her developmental delay (developmental age was 14 months at age 22 months). A repeat CT scan (Fig. 1D) after 7 months of therapy was normal, and EEG findings had also normalized.

Results

The results of the CT and MR examinations of our eight patients are presented in Table 2. While the findings were

TABLE 2: Eight Patients with Cofactor-Dependent PKU: CT and MR Findings

Case No.	Age	Sex	CT Findings			MR
			Ventricles	Sulci/Fissures	White Matter	White Matter
1	5 yr	M	++	++	N	
	+11 mo ^a		++	++	+	
	+7 mo ^b		++	++	+	
2	2 mo	F	N	+	N	
	+5 mo		N	++	N	
	+6 mo		+	++	N	
	+7 mo ^b		N	N	N	N
3	5 mo	M	N	+	N	
	+7 mo ^b		N	+	N	
4	6 mo	M	N	N	N	
5	14 mo	F	N	N	+	
6	22 mo	M	+	++	+++	+++
7	4 yr	F	+	++	N	
8	4 mo	F	N	N	++	++

Note.—Size of ventricles and sulci/fissures was subjectively graded as either normal (N) or slightly (+), significantly (++) or markedly (+++) increased. White matter was classified as normal (N), or with signs of slight (+), moderate (++), or advanced (+++) white matter disease.

^a Denotes interval between consecutive CT/MR examinations.

^b After 7 months of therapy.

TABLE 1: Eight Patients with Cofactor-Dependent PKU: Clinical Findings

Case No.	Parents Consanguineous	Age at Diagnosis	Estimated Developmental Age	Seizures	Leg Reflexes	Tone	
						Trunk	Limbs
1	1st cousins	5 yr ^a	<2 mo at 4 yr	Myoclonic	+	—	++
2	1st cousins	13 mo ^a	1–3 mo at 13 mo	Myoclonic	++	—	++
3	1st cousins	12 mo	4 mo at 5 mo	No	++	—	+
4	1st cousins	6 mo ^b	0–2 mo at 6 mo	No	++	—	+
5	1st cousins	14 mo	3 mo at 14 mo	Myoclonic	Babinski +	—	++
6	Not related	22 mo	0 mo at 22 mo	No	Babinski +	—	++
7	1st cousins	4 yr	<1 mo at 18 mo	Choreoathetosis	++	—	++
8	1st cousins	4 mo ^b	<2 mo at 4 mo	Myoclonic	+	—	N

Note.—Reflexes were graded as normal (N) or slightly (+) or markedly (++) increased. Tone was graded as normal (N), slightly (—), or markedly (—) decreased; or slightly (+) or markedly (++) increased.

^a Full siblings.

^b Half siblings.

discrete in most of the patients, only one CT examination was evaluated as entirely normal (case 4). In two patients the only finding was slight prominence of sulci and fissures (Fig. 1A). In another three patients the widening was significant and involved the ventricular system as well as the fissures and sulci (Fig. 2). Slight to significant white matter disease was seen as an isolated finding in two patients; severe white matter disease was found in only one patient (case 6, Fig. 3), who also showed significant loss of brain volume. This child came to the hospital in extremely poor condition and died before the diagnosis had been verified and therapy started. An MR performed in two of the patients confirmed white matter disease.

Even if there was a tendency for the older children to exhibit more severe CT pathology, no clear correlation between age and CT findings was present.

One 2-year-old patient with untreated classical PKU was also seen during this period. This patient at CT and MR (Fig. 4) had signs of significant white matter disease; the ventricles, fissures, and sulci were normal.

Discussion

Considering the relatively frequent occurrence of PKU and the fact that the disease is characterized by cerebral complications, we were surprised to find only one report on the CT findings [4] in classical PKU, none regarding cofactor-dependent HPA, and none concerning MR findings in PKU. Histopathologic studies in classical PKU [5] have demonstrated extensive white matter changes with spongy degeneration of the myelin and foci of demyelination, later followed by glial reaction and by accumulation of lipid material. One would thus expect to see white matter disease at CT, but Behbehani et al. [4], who reported 14 patients with classical PKU (six of whom were untreated until 2–8 years of age and showed severe mental retardation), found white matter disease in only one patient. This patient had, however, also suffered from severe neonatal asphyxia, which was thought to be the cause of the white matter disease.

The therapeutic goal in cofactor-dependent HPA is twofold: to control the blood level of phenylalanine and to normalize

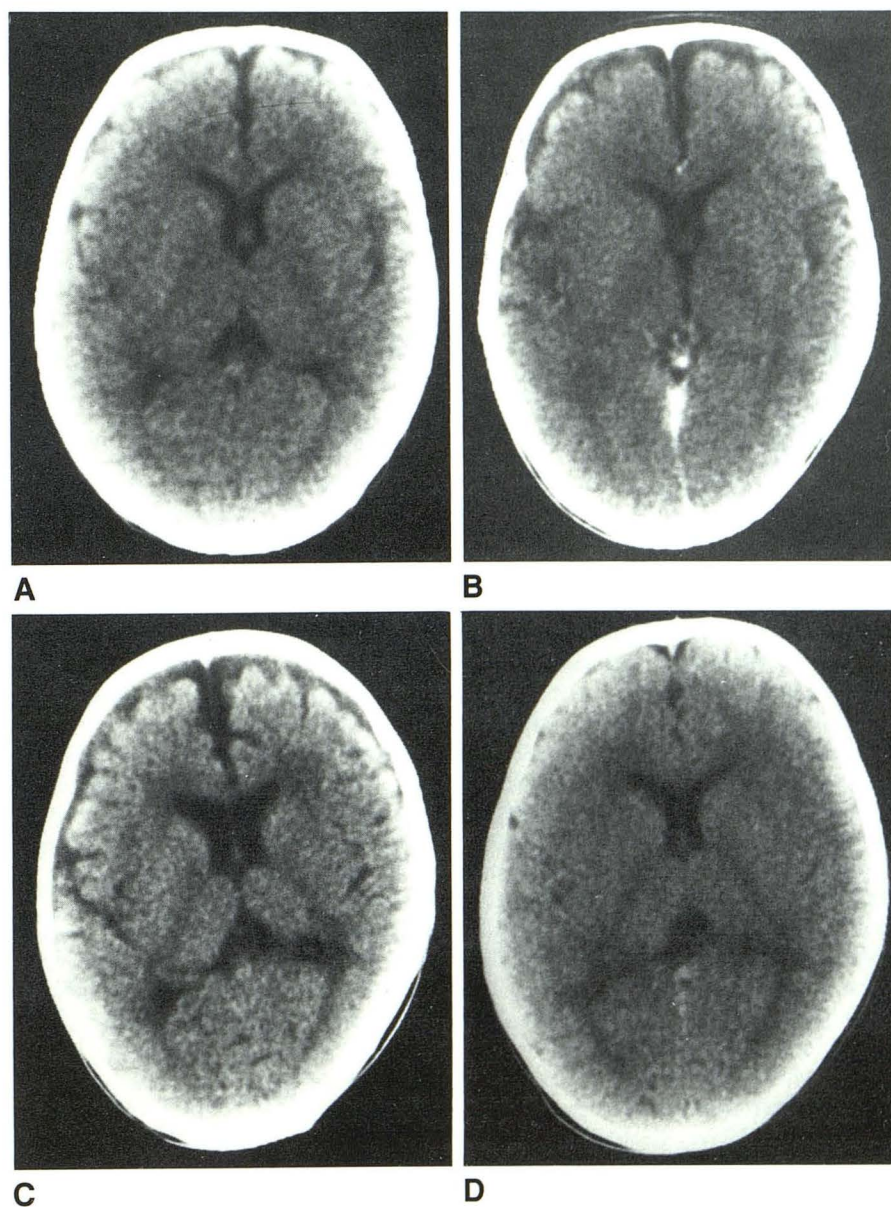


Fig. 1.—Case 2. Girl with cofactor-dependent PKU.

A, CT at age 2 months shows slight prominence of frontal sulci and interhemispheric fissure.

B, CT at age 7 months shows further widening of sulci.

C, CT at age 13 months shows marked widening of sulci and fissures, and also some ventricular dilatation.

D, At age 20 months, after 7 months of therapy, CT is normal.

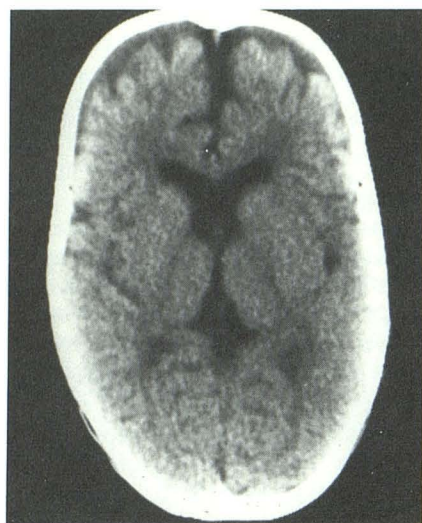
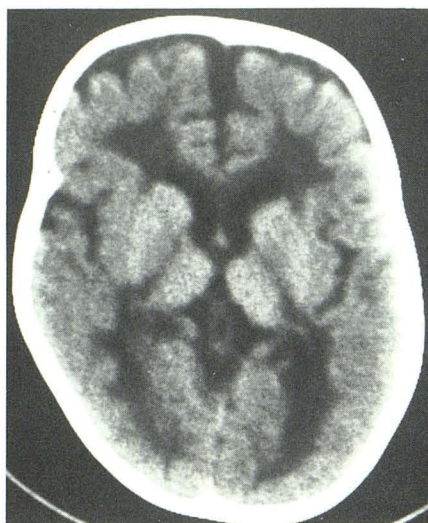
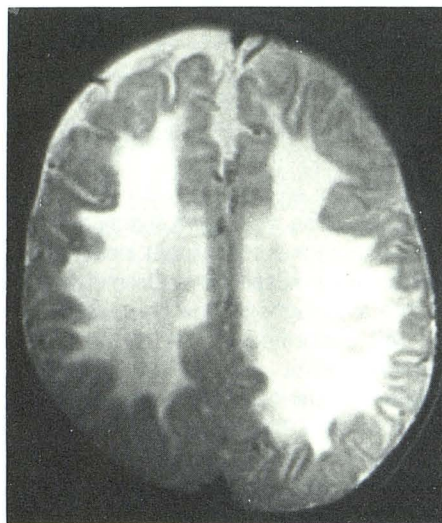


Fig. 2.—Case 7. CT shows significant widening of sulci and slight widening of ventricles in 4-year-old girl with cofactor-dependent PKU.

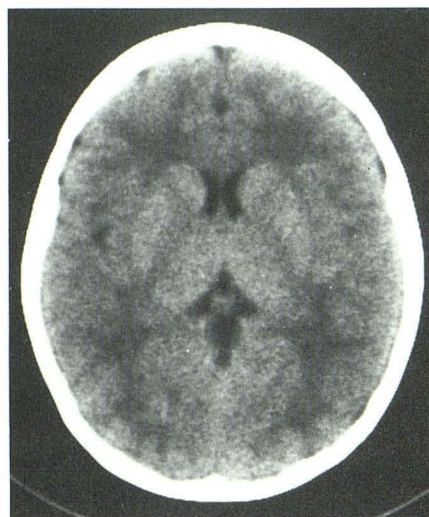


A



B

Fig. 3.—Case 6. 22-month-old boy with cofactor-dependent PKU and severe clinical manifestations. A and B, CT (A) and T2-weighted MR image, 2000/80 (B), show severe white matter disease, significant widening of the sulci, and slight ventricular dilatation.



A



B

Fig. 4.—2-year-old boy with untreated classical PKU (not included in the series).

A and B, CT (A) and T2-weighted MR image, 2000/80 (B), show moderate white matter disease.

the monoamine neurotransmission. Ideally, this would be achieved by administering the deficient cofactor; however, in practice, this has proved insufficient and the monoamine precursors L-dopa and 5-hydroxytryptophan, as well as carbidopa (given to bypass the impaired activity of tyrosine and tryptophan hydroxylase), need to be administered [1], possibly in combination with a synthetic cofactor. The response to such therapy may be dramatic, as illustrated in our case.

A significant clinical improvement after therapy was also seen in the other six patients treated—this is also the experience of other researchers [1, 6], even if some doubts have arisen concerning the long-term results [2]. The normalization of the CT findings in our case 2 stresses the importance of an early diagnosis. Since definite brain damage develops if therapy is delayed (as in our case 1), it is mandatory that all children who at screening for PKU present with even slightly elevated serum phenylalanine levels, be evaluated for cofactor deficiency [1, 6].

From a radiologic point of view, cofactor-dependent PKU should be kept in mind as a possible cause when in spite of

severe clinical findings the CT examination shows only discrete pathology. Furthermore, PKU—either classical or cofactor-dependent—should be added to the list of possible causes of white matter disease seen at CT or MR.

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