Dihydropteridine reductase deficiency (DHPR) is required for resynthesis of tetrahydrobiopterin (BH4), the essential cofactor for aromatic amino acid hydroxylases, which are the rate-limiting enzymes for the catabolism of phenylalanine and the biosynthesis of biogenic monoamines (figure 1).1 Hyperphenylalaninemia is observed in all forms of DHPR deficiency. Furthermore, unless supplementation with levodopa and 5-hydroxytryptophan (5HTP), the precursors of dopamine and serotonin, is introduced, patients with the severe form of DHPR deficiency exhibit an encephalopathy within several months of life, leading to death in childhood.1 No detailed description of the long-term outcome of treated patients with severe DHPR deficiency has been made to date.

Case report. The patient is registered in the BIODEF database (www.bh4.org) under the number 135. He was born in 1976 to first cousin parents of Portuguese ancestry. Hyperphenylalaninemia was discovered after neonatal screening. A phenylalanine-poor diet was started and phenylalaninemia normalized. At 1 month, the child was pale and somnolent. He made few movements, hypersalivated, and could not fix his eyes. Neopterin and biopterin in urine-spotted filters were 28 pmol/5-mm disc (16 pmol/5-mm disc in controls) and 80 pmol/5-mm disc (3 pmol/5-mm disc in controls). CSF 5-hydroxyindoleacetic acid level was 6 pmol/5-mm disc (normal >95 ng/mL; homovanillic acid not measured). Undetectable DHPR activity in liver biopsy, fibroblasts, and erythrocytes led to the diagnosis of severe DHPR deficiency (figure 1). Gene sequencing subsequently revealed a homozygous mutation (W108G) in exon 4 of the QDPR gene. Levodopa (15 mg/kg/day) in addition to carbidopa (1.25 mg/kg/day) and 5-HTP (4 mg/kg/day) treatment was started at age 3 months. To avoid intracerebral folate deficiency, folinic acid was added when he was age 6 years.1 At age 4 months, the patient could hold his head up or manipulate objects. At age 6 months, he was considered normal. The subsequent psychomotor development was slightly delayed, however: he walked at age 2.5 years, made his first sentences at age 4, learned to write at age 9, and to read at age 13. He was not able to undertake occupational training and is currently working as a town hall technician.

From age 9, the patient experienced twice a year transient episodes of acute parkinsonism accompanied by neurovegetative dysfunction. Each episode lasted from several minutes to several hours until levodopa administration, which led to a rapid and complete recovery. When he was age 11, he made two suicide attempts because of acute depression. At age 29, no parkinsonian symptoms or dyskinesia was observed with levodopa/benserazide (500 mg/125 mg/day), 5HTP (500 mg/day), and folinic acid (75 mg/day) treatment. Cognitive efficiency was considered poor, including attention deficit and a dysexecutive syndrome: Mini-Mental State score was 21/30, Mattis Dementia Rating Scale score was 117/144, and IQ (measured with the Raven 47 Colored Progressive Matrices Scale) was 67. Following an 18-hour treatment discontinuation, a typical acute episode of parkinsonism (severe akinesia, rest tremor, bilateral ptosis, hypersalivation) was observed, which resolved 15 minutes after oral intake of levodopa/benserazide (200 mg/50 mg).

When he was age 29, two PET studies were performed.2 Striatal binding of [11C]PE2I, a highly specific radioligand of the neuronal membrane dopamine transporter, was similar to values obtained from healthy volunteers, indicating no dopaminergic neuronal loss. Striatal binding of [11C]raclopride, a high-affinity D2 dopamine receptor antagonist, was increased by 25% vs control values (figure 2).

Discussion. DHPR deficiency is a rare condition in which the endogenous synthesis machinery of dopamine and serotonin is defective. This is in contrast to levodopa-responsive dystonia due to heterozygote mutations in the GTP cyclohydrolase 1 gene, where an endogenous synthesis of monoamines remains. Although some adult patients with a mild form of DHPR deficiency have been described,4 the severity of the enzymatic deficiency in our patient is suggested by the early neurologic deterioration preceding the diagnosis and by the biochemical analysis that revealed no residual enzyme activity. Despite the severity of the enzymatic deficiency and the long duration of the disease, the patient had no signs of monoamine deficiency under long-term replacement therapy, except 1) levodopa-responsive episodes of parkinsonism and neurovegetative dysfunction most likely resulting from dopamine and noradrenaline deficiency and 2) two episodes of acute depression compatible with brain serotonin and noradrenaline deficiency.

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deficiency. The favorable outcome in this patient is most likely due to the early diagnosis and treatment with levodopa and 5-HTP.

In contrast to patients with Parkinson disease who develop levodopa-induced motor complications, our patient had no daily motor fluctuations or dyskinesias after several decades of levodopa treatment. The absence of levodopa-induced motor complications most likely results from the absence of dopamine neuron loss, as inferred from normal or high neopterin. Note that exogenous levodopa and 5-hydroxytryptophan (5HTP) are transformed into dopamine and serotonin, by dopa decarboxylase, which is not BH4 dependent. AADC = aromatic l-aminoacid decarboxylase; NH2TP = dihydronopterin triphosphate; 6-PTP = 6-pyruvoyl tetrahydropterin; SR = sepiapterin reductase; qBH2 = quinonoid dihydropterin; NO = nitric oxide; VMA = vanillylmandelic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol.

that the “priming hypothesis” does not apply in patients with an intact nigrostriatal dopamine system. Interestingly, PET imaging in our patient revealed an up-regulation of D2 dopamine receptors. This up-regulation very likely resulted from a compensatory mechanism due to dopamine synthesis deficiency, as also observed in patients with levodopa-responsive dystonia due to GTP cyclohydrolase 1 mutations.

There is still a debate whether the long-term use of levodopa is toxic for dopaminergic neurons. The fact that PET imaging did not reveal dopaminergic loss in our patient despite 30 years of treatment suggests that levodopa per se is not toxic in vivo in humans. This confirms a previous report in a patient with essential tremor who received levodopa for 4 years but did not exhibit any neuronal loss in the substantia nigra. Interestingly, in addition to our case, five adult patients with the severe form of 6-pyruvoyl tetrahydropterin synthase deficiency, another and more common inborn biotinoprotein synthesis defect, have been reported. Among these patients, only those treated before the first year of life had a favorable outcome, whereas patients treated after this period exhibited a severe encephalopathy characterized by the presence of disabling motor fluctuations and dyskinesias. These observations and our case report suggest that early replacement therapy

Figure 1. Monoamine and tetrahydrobiopterin biosynthesis and regeneration (adapted from ref. 1). Hallmarks of dihydropteridine reductase (DHPR) deficiency are hyperphenylalaninemia, low CSF tetrahydrobiopterin (BH4), dopamine, serotonin, homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5HIAA), high CSF dihydrobiopterin (BH2), with normal or high neopterin. Note that exogenous levodopa and 5-hydroxytryptophan (5HTP) are transformed into dopamine and serotonin, by dopa decarboxylase, which is not BH4 dependent. AADC = aromatic l-aminoacid decarboxylase; NH2TP = dihydronopterin triphosphate; 6-PTP = 6-pyruvoyl tetrahydropterin; SR = sepiapterin reductase; qBH2 = quinonoid dihydropterin; NO = nitric oxide; VMA = vanillylmandelic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol.

Figure 2. Comparison of the mean binding potential (BP) values (mean ± SD) calculated for [11C]PE2I and for [11C]raclopride, for the caudate and putamen in healthy control subjects and in our patient. Two PET studies were performed1 after overnight levodopa interruption (approximately 16 hours of interruption). Striatal BP of [11C]PE2I, a highly specific radioligand of the neuronal membrane dopamine transporter, was similar to values obtained from healthy volunteers, indicating no dopaminergic neuronal loss (11 healthy controls; mean ± SD age = 45 ± 7 years; mean ± SD BP = 4.5 ± 0.5 for caudate and 4.4 ± 0.5 for putamen; patient: caudate BP = 4.5 and putamen BP = 4.7). Striatal binding of [11C]raclopride, a high-affinity D2 dopamine receptor antagonist, was increased by about 25% vs control values (nine healthy controls; mean ± SD age = 29 ± 8 years; mean ± SD BP = 2.8 ± 0.3 for caudate and 3.0 ± 0.2 for putamen; patient: caudate BP = 3.6 and putamen BP = 3.6).
with levodopa and 5HTP might have protective effects on brain neurons during development.

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