

this study is not a true prevalence study because the study group was small, not population-based, and no control group was included.¹⁹

In summary, we examined for the first time the occurrence of extrapyramidal disease in our large family with RLS and *Parkin* mutations. In the “RLS branch” of our family, the pattern of inheritance, along with early age of onset, clearly suggested a genetic cause of RLS. *Parkin* mutations in approximately half of our RLS patients obviously had no influence on the RLS phenotype in this family. This finding was confirmed in the second smaller RLS pedigree with affected family members with and without a *Parkin* mutation. The role of *Parkin* mutations in RLS needs to be further investigated in other families and by case–control studies. In our large family, linkage to all three known loci for RLS was excluded, providing evidence for at least one additional RLS gene that will be searched for by a genome-wide linkage analysis.

Acknowledgments: We thank the family members who participated in this study. We also thank Dr. Claudia Trenkwalder for helpful discussion of the manuscript. This work was supported by grants from the South Tyrolean PD association (SA), the Deutsche Forschungsgemeinschaft (KI 1134/3-1), the VolkswagenStiftung and the University of Lübeck.

REFERENCES

- Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson's disease and restless legs syndrome. *Arch Neurol* 2002;59:421–424.
- Krishnan P, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. *Mov Disord* 2003;18:181–185.
- Garcia-Borreguero D, Odin P, Serrano C. Restless legs syndrome and PD: a review of the evidence for a possible association. *Neurology* 2003;61(Suppl. 3):S49–S55.
- Desautels A, Turecki G, Montplaisir J, et al. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet* 2001;69:1266–1270.
- Bonati MT, Ferini-Strambi L, Aridon P, et al. Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain* 2003;126:1485–1492.
- Chen S, Ondo WG, Rao S, et al. Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. *Am J Hum Genet* 2004;74:876–885.
- Hedrich K, Djarmati A, Schäfer N, et al. *DJ-1* mutations are less frequent than *Parkin* mutations in early-onset Parkinson's disease. *Neurology* 2004;62:389–394.
- Klein C, Pramstaller PP, Kis B, et al. *Parkin* deletions in a family with adult-onset, tremor-dominant Parkinsonism: expanding the phenotype. *Ann Neurol* 2000;48:65–71.
- Hedrich K, Kann M, Lanthaler AJ, et al. The importance of gene dosage studies: mutational analysis of the parkin gene in early-onset parkinsonism. *Hum Mol Genet* 2001;16:1649–1656.
- Kock N, Culjkovic B, Maniak S, et al. Mode of inheritance and susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet* 2002;71:205–208.
- Allen RP, Picchietti D, Hening W, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institute of Health. *Sleep Med* 2003;4:101–119.
- Allen RP, Earley CJ. Validation of the Johns Hopkins restless legs severity scale. *Sleep Med* 2001;2:239–242.
- The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;4:121–132.
- O'Connell JR, Weeks DE. The VITESSE algorithm for rapid exact multilocus linkage analysis via genotype set-recording and fuzzy inheritance. *Nat Genet* 1995;11:402–408.
- Hedrich K, Marder K, Harris J, et al. Evaluation of 50 probands with early-onset Parkinson's disease for *Parkin* mutations. *Neurology* 2002;58:1239–1246.
- Tan E, Lum S, Wong M. Restless legs syndrome in Parkinson's disease. *J Neurol Sci* 2002;196:33–36.
- Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol* 2001;18:128–147.
- Pittock SJ, Parrett T, Adler CH, et al. Neuropathology of primary restless legs syndrome: absence of specific tau- and alpha-synuclein pathology. *Mov Disord* 2004;19:695–699.
- Walters AS. A preliminary look at the percentage of patients with restless legs syndrome who also have Parkinson's disease, essential tremor or Tourette syndrome in a single practice. *J Sleep Res* 2003;12:343–345.

Long-Term Follow-Up and Adult Outcome of 6-Pyruvoyl-Tetrahydropterin Synthase Deficiency

Emmanuel Roze, MD,^{1,2*} Marie Vidailhet, MD,^{1,3}
Nenad Blau, MD, PhD,⁴ Lisbeth Birk Moller, PhD,⁵
Diane Doummar, MD,⁶
Thierry Billelte de Villemeur, MD,⁶ and
Anne Roubergue, MD^{1,6}

¹Department of Neurology, Saint-Antoine Hospital, Paris, France; ²CNRS UMR7102, Paris, France; ³INSERM U679, Paris, France; ⁴Division of Clinical Chemistry and Biochemistry, University Children's Hospital, Zurich, Switzerland; ⁵John F. Kennedy Institute, Glostrup, Denmark; ⁶Department of Child Neurology, Trousseau Hospital, Paris, France

Video



Abstract: Little information is available on the long-term course and adult outcome of patients with 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency. We describe the course of a 32-year-old woman with hypotonia, dystonia, cho-

This article includes Supplementary Video, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat>

*Correspondence to: Dr. Emmanuel Roze, Service de Neurologie, Hôpital Saint Antoine, 184 rue du Faubourg Saint-Antoine, 75571 Paris cedex 12, France. E-mail: emmanuel.roze@sat.aphp.fr

Received 7 April 2005; Revised 2 June 2005; Accepted 12 June 2005

Published online 13 September 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20699

reathetosis, mental retardation, behavioral disturbances, and incomplete puberty due to PTPS deficiency. From the age of 6 months she developed progressive hypotonia and choreoathetoid movements despite good control of hyperphenylalaninemia. Tetrahydrobiopterin deficiency was diagnosed at age 3 years. She had a dramatic response to L-dopa, which persisted at a stable dose for 29 years. Reducing the L-dopa dose led to severe axial hypotonia and limb dystonia, and increasing it led to florid abnormal movements and behavioral disorders. This report illustrates the role of dopamine modulation in motor, psychiatric, and endocrine functions. © 2005 Movement Disorder Society

Key words: 6-pyruvoyl-tetrahydropterin synthase deficiency; tetrahydrobiopterin deficiency; malignant hyperphenylalaninemia; symptomatic dystonia; choreoathetosis

Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency is an autosomal recessive disorder resulting in severe neurological manifestations, including psychomotor retardation, hypotonia, seizures, and movement disorders.¹ This enzyme is required to produce tetrahydrobiopterin (BH4), which is an essential cofactor in the biosynthesis of dopamine, serotonin, and nitric oxide (NO; Fig. 1). As most of these symptoms are likely related to neurotransmitter depletion, and as BH4 may not readily enter the brain, patients with PTPS deficiency receive L-dopa and 5-hydroxytryptophan (5-HTP) in addition to BH4 supplementation.¹

The prompt neurological improvement induced by this treatment is well known.² By contrast, there are few reports on long-term treatment efficacy and adult outcome of patients treated since infancy and early childhood.^{3,4} Here we describe the long-term outcome of a

32-year-old woman who was the second reported patient with PTPS deficiency in 1976.⁵ We focus on the nature of her movement disorders and her long-term L-dopa responsiveness.

CASE REPORT

This 32-year-old woman was the first child of two unrelated French parents. At age 7 days, routine neonatal screening revealed elevated phenylalaninemia (1,800 $\mu\text{mol/L}$; normal value, < 120 $\mu\text{mol/L}$). From age 14 days, she was given a low-phenylalanine diet, leading to a sustained reduction in phenylalaninemia to below 300 $\mu\text{mol/L}$. She received no drug treatment until age 3 years. At age 1 month, physical examination was normal except for a poor response to stimuli and mild hypotonia. At age 6 months, she showed reduced spontaneous motility, marked axial hypotonia, diffuse myoclonic jerks, "lead-pipe" limb rigidity, and abnormal movements, including pedaling movements of the legs and choreoathetoid arm movements. Tendon reflexes were brisk, without Babinski's sign. She started to drool and have swallowing difficulties, resulting in recurrent chest infections. Between age 1 and 3 years, both voluntary and abnormal movements disappeared, except for oculogyric crises. She was indifferent to her surroundings and made no eye contact. She had multiple episodes of hyperthermia or hypothermia, lasting few hours, and generalized tonic-clonic seizures. BH4 deficiency was diagnosed at age 3 years, based on biopterin derivative assay after a phenylalanine loading test. Enzymatic studies showed that erythrocyte PTPS activity was only 14% of normal,

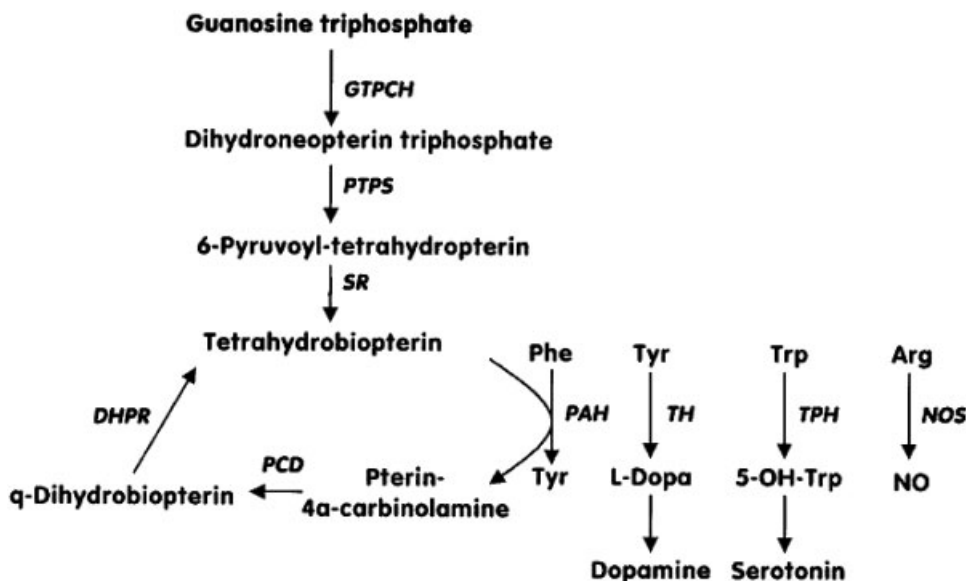


FIG. 1. Biosynthesis and regeneration of tetrahydrobiopterin. 5-OH-Trp, 5-hydroxy tryptophan; Arg, arginine; DHPR, dihydropteridine reductase; GTPCH, guanosine triphosphate cyclohydrolase 1; NO, nitric oxide; NOS, nitric oxide synthase; PAH, phenylalanine-3-hydroxylase; PCD, pteridin-4a-carbinolamine dehydratase; Phe, phenylalanine; PTPS, 6-pyruvoyl-tetrahydropterin synthase; SR, sepiapterin reductase; TH, tyrosine-4-hydroxylase; THP, tryptophan-5-hydroxylase; Trp, tryptophan; Tyr, tyrosine.

confirming that BH4 deficiency was due to PTPS deficiency. Genetic studies (performed at age 32) showed compound heterozygosity for the mutations IVS1-3G>A and 297C>A (Y99X) in the PTPS gene. Neurotransmitter precursor replacement therapy with L-dopa (16 mg/kg/day) and 5-HTP (20 mg/kg/day) was started. It resulted in a dramatic clinical improvement, with reappearance of spontaneous voluntary movements and tendon reflexes and less hypotonia. She was also able to make eye contact and to rotate her head in response to noise. During the first weeks of this treatment, she had generalized dyskinesia, which was controlled by reducing and fractionating the daily L-dopa dose. She no longer had swallowing disorders, oculogyric crises, thermal dysregulation, or generalized seizures. She remained moderately hypotonic at age 5 years, but was able to sit for a few minutes at a time. Her motor skills improved and she was able to manipulate objects, albeit with poor coordination. She was able to interact with her family. At age 6 years, interruption of neurotransmitter replacement therapy for new metabolic studies was followed by a severe relapse, with major hypotonia, drowsiness, life-threatening swallowing disorders, respiratory failure, and cardiac arrhythmia. Neurotransmitter replacement therapy was resumed, accompanied by BH4 therapy, which had not previously been available. BH4 administration (20 mg/day) allowed the neurotransmitter doses to be reduced by 70% for the same clinical response and maintained the phenylalaninemia below 300 $\mu\text{mol/L}$ without a low-phenylalanine diet. After age 6 years, her psychomotor development remained markedly retarded despite optimal combination therapy with BH4 (25 mg/day), L-dopa (5 mg/kg/day), and 5-HTP (4 mg/kg/day). Puberty was late and incomplete. She reached only Tanner stage III, at age 16, and never had menstrual cycles. At age 32, her height was 159 cm, her weight was 39 kg, and her head circumference was 53 cm. From age 6 to 32 years, she remained highly dependent on her treatment, to which her response remained remarkably stable over the years. Variation of symptoms were observed: (1) When treatment efficacy was maximal (*on* stage; see Video) she could sit upright in a corset, with contributory trunk muscle tone but with residual hypotonia of the neck. She could move all four limbs, albeit with poor coordination. She had moderate generalized dystonia with axial hypotonia and superimposed choreoathetoid movements of the limbs, neck, and face. She was communicative and could utter a few words. (2) At the end of effect of each L-dopa dose (5 hours after intake) she had a worsening of axial hypotonia, akinesia and severe fixed generalized dystonia. Because of these end-of-dose motor fluctuations, she required shorter intervals between

doses. (3) A 100-mg reduction of the daily L-dopa dose led to severe hypotonia and swallowing difficulties. A period of insufficient L-dopa absorption due to recurrent vomiting was associated with recurrence of severe disorders, including major hypotonia, drowsiness, and seizures. (4) A 100-mg increase in the daily L-dopa dose led to more abnormal movements and behavioral disorders including aggressiveness and sleep disturbances. Feeding was transiently withheld during an episode of severe purulent pleurisy, leading to increased drug absorption and extremely severe ballistic dyskinesia and psychomotor agitation, which resolved following the resumption of normal feeding and recovery from the infection.

At age 32 her condition is stable. The daily dose of L-dopa (300 mg) and the clinical response have been stable for the last 10 years. The prolactin level, assayed to investigate her primary amenorrhea, was elevated (103 $\mu\text{g/L}$; normal, < 20 $\mu\text{g/L}$).

DISCUSSION

We describe the 32-year clinical course of a patient with the typical severe form of PTPS deficiency, which was treated with neurotransmitter replacement therapy from age 3 years and BH4 supplementation from age 6 years. In addition to severe psychomotor retardation, the main features in adulthood were generalized dystonia with axial hypotonia and choreoathetoid movements of the limbs, neck, and face. Generalized dystonia has previously been reported in two cases of PTPS deficiency diagnosed in adulthood.^{6,7} Choreoathetoid movements were not mentioned in these two adults but have been observed in children.^{4,8} Axial hypotonia is also a common feature in children with PTPS deficiency.¹ Diurnal symptom fluctuation has been described as both spontaneous and related to L-dopa intake.^{6,7,9} Our patient's diurnal fluctuations appeared to be related mainly to L-dopa intake.

Our patient had a dramatic, stable, and sustained response to L-dopa with 29 years of follow-up (from age 3 years to 32 years). A similar long-term response has been reported in children.⁹ It was also briefly reported in a group of 6- to 18-year-old patients treated after neonatal screening.³ There are only two reported adult cases, with shorter follow-up (16 and 19 years, respectively).⁴ The first patient with generalized hypotonia and drowsiness did not respond to L-dopa but was markedly improved by BH4 supplementation. The second patient, who had parkinsonism, oculogyric crises, and hypotonia, developed critical symptoms of L-dopa overdose during treatment, with marked dyskinetic movements; various L-dopa protocols failed to improve the patient's condition. Patients

with dopa-responsive dystonia (DRD) due to a heterozygous mutation of the GTP cyclohydrolase 1 (GTPCH1) gene also have a sustained response to L-dopa and are treated with stable doses over decades.¹⁰ The pattern of movement disorders in our patient differed from the classical form of DRD. In addition to dystonia, her movement disorders included (1) choreoathetoid movements and myoclonia associated with marked hypotonia from disease onset, prior to L-dopa treatment; (2) marked axial hypotonia and severe dystonia of the limbs during insufficient L-dopa dosing; (3) improved motility, less hypotonia, and fewer choreoathetoid movements at maximal L-dopa efficacy; and (4) diffuse severe choreic and ballistic dyskinesia during excessive L-dopa exposure. This illustrates that slight variations in dopamine levels can lead to the expression of movement disorders ranging from dystonia to chorea and ballism, in the absence of dopamine denervation.

Despite good adherence to optimal available therapy, our patient had a poor clinical outcome with severe psychomotor retardation, persistent muscle tone disorders, and unrelenting movement disorders. However, late diagnosis of PTPS deficiency, as in our patient (at the age of 3 years), has been linked to more severe neurological impairment and to a poorer response to treatment; likewise, early treatment has been shown to improve the IQ.^{2,11} Most patients diagnosed by neonatal screening and treated from birth have normal psychomotor development or only mild mental retardation and subtle motor dysfunction.^{2–4,11} However, few patients in whom treatment was started in the neonatal period had severe neurological disease.^{12,13} It is possible that NO and serotonin deficiency due to impaired BH4 biosynthesis may cause abnormal perinatal CNS development, contributing to the poor outcome of some patients.^{14,15}

Hyperprolactinemia resulting from dopamine deficiency in the hypothalamus may explain why our patient had only partial puberty. Elevated prolactinemia has also been reported elsewhere in patients with PTPS deficiency.^{1,12} Dopamine released by tuberoinfundibular neurons of the arcuate nucleus of the hypothalamus acts as a prolactin-inhibiting factor on the median eminence. Conversely, prolactin is an accurate index of hypothalamic dopamine content and may be used to monitor dopamine therapy.¹² Our patient also had psychiatric manifestations. During excessive dopamine stimulation, she developed transient behavioral disorders, which were probably dopamine-mediated (mesolimbic circuits), as they can also occur during antiparkinsonian drug therapy of Parkinson's disease. In conclusion, this case illustrates the roles of dopamine in modulating motor, psychiatric, and endocrine functions.

LEGEND TO THE VIDEO

Generalized dystonia, choreoathetoid movements, and axial hypotonia 2 hours after intake of 100 mg of L-dopa.

Acknowledgments: This study was supported by the INSERM National Network on Dystonia. We thank Dr. Françoise Rey for referring the patient and Michel Laudon for helping with the patient's clinical care.

REFERENCES

- Blau N, Thony B, Cotton R, Hyland K. Disorders of tetrahydrobiopterin and related biogenic amines. In: Scriver CR, Sly WR, Childs B, et al., editors. *The metabolic and molecular basis of inherited disease*, 8th ed. New York: McGraw-Hill Professional; 2001. p 1725–1776.
- al Aqeel A, Ozand PT, Gascon G, et al. Biopterin-dependent hyperphenylalaninemia due to deficiency of 6-pyruvoyl tetrahydropterin synthase. *Neurology* 1991;41:730–737.
- Kao CD, Niu DM, Chen JT, et al. Subtle brain dysfunction in treated 6-pyruvoyl-tetrahydropterin synthase deficiency: relationship to motor tasks and neurophysiological tests. *Brain Dev* 2004; 26:93–98.
- Dudsek A, Roschinger W, Muntau AC, et al. Molecular analysis and long-term follow-up of patients with different forms of 6-pyruvoyl-tetrahydropterin synthase deficiency. *Eur J Pediatr* 2001;160: 267–276.
- Leeming RJ, Blair JA, Rey F. Biopterin derivatives in atypical phenylketonuria. *Lancet* 1976;1:99–100.
- Tanaka K, Yoneda M, Nakajima T, Miyatake T, Owada M. Dihydrobiopterin synthesis defect: an adult with diurnal fluctuation of symptoms. *Neurology* 1987;37:519–522.
- Hanihara T, Inoue K, Kawanishi C, et al. 6-pyruvoyl-tetrahydropterin synthase deficiency with generalized dystonia and diurnal fluctuation of symptoms: a clinical and molecular study. *Mov Disord* 1997;12:408–411.
- Factor SA, Coni RJ, Cowger M, Rosenblum EL. Paroxysmal tremor and orofacial dyskinesia secondary to a biopterin synthesis defect. *Neurology* 1991;41:930–932.
- Tanaka Y, Matsuo N, Tsuzaki S, Araki K, Tsuchiya Y, Niederwieser A. *On-off* phenomenon in a child with tetrahydrobiopterin deficiency due to 6-pyruvoyl tetrahydropterin synthase deficiency (BH4 deficiency). *Eur J Pediatr* 1989;148:450–452.
- Harwood G, Hierons R, Fletcher NA, Marsden CD. Lessons from a remarkable family with dopa-responsive dystonia. *J Neurol Neurosurg Psychiatry* 1994;57:460–463.
- Chien YH, Chiang SC, Huang A, et al. Treatment and outcome of Taiwanese patients with 6-pyruvoyltetrahydropterin synthase gene mutations. *J Inher Metab Dis* 2001;24:815–823.
- Birnbacher R, Scheibenreiter S, Blau N, Bieglmayer C, Frisch H, Waldhauser F. Hyperprolactinemia, a tool in treatment control of tetrahydrobiopterin deficiency: endocrine studies in an affected girl. *Pediatr Res* 1998;43(4 Pt. 1):472–477.
- Szeinberg A, Cohen B. malignant hyperphenylalaninemia due to defective synthesis of dihydrobiopterin. *Adv Clin Enzymol* 1987; 5:74–80.
- Murata Y, Masuko S. Developing patterns of nitric oxide synthesizing neurons in the rat striatum: histochemical analysis. *Brain Res Dev Brain Res* 2003;141:91–99.
- Luo X, Persico AM, Lauder JM. Serotonergic regulation of somatosensory cortical development: lessons from genetic mouse models. *Dev Neurosci* 2003;25:173–183.