

Long-term course of L-dopa-responsive dystonia caused by tyrosine hydroxylase deficiency

A. Schiller, MD; R.A. Wevers, PhD; G.C.H. Steenbergen, PhD; N. Blau, PhD; and H.H. Jung, MD

Abstract—The authors report the long-term course of two siblings with L-dopa responsive dystonia (DRD) associated with a compound heterozygous mutation in the tyrosine hydroxylase (TH) gene. Both siblings manifested with lower-limb onset generalized DRD and had a sustained response to low-dose L-dopa therapy for over 35 years. Although the L-dopa therapy was delayed up to 20 years after disease onset, there were no cognitive or neurologic sequelae of the long-term catecholamine deficit.

NEUROLOGY 2004;63:1524–1526

L-Dopa responsive dystonias (DRD) are a heterogeneous group of movement disorders. Autosomal dominant DRD or Segawa syndrome (MIM # 128230) is caused by mutations of the GTP cyclohydrolase I gene (*GCH1*), and is characterized by childhood-onset DRD with diurnal fluctuations, little progression in adulthood, and excellent long-term response to L-dopa.^{1,2} Autosomal recessive DRD (MIM # 605407) is caused by mutations of the tyrosine hydroxylase (*TH*) gene. *TH* is the rate limiting enzyme of the biosynthesis of the catecholamines dopamine, epinephrine, and norepinephrine.³ *TH* deficiency usually manifests in the first 3 years of the life with progressive generalized dystonia and parkinsonism.^{4–7} L-Dopa response is variable, ranging from complete remission to lack of responsiveness in the context of a progressive neurodegenerative disease.^{5–7}

Herein, we describe two brothers with a novel compound heterozygous mutation in the *TH* gene who had infantile-onset generalized dystonia with a complete response to low-dose L-dopa therapy over many decades.

Case reports. *Patient 1.* The older brother of a nonconsanguineous family was born in 1950. His initial psychomotor development was normal. After the age of 3 years, increasing walking difficulties, falls, augmented muscle tone, and dystonic posturing developed, making him wheelchair-bound within 10 years. At the age of 24 years, neurologic examination revealed severe generalized dystonia. A therapeutic trial with L-dopa/benserazide 200/50 mg had a dramatic effect. After 7 days, muscle tone, hand functions, and gait normalized. Over the following years, L-dopa medication had a sustained efficacy. At the age of 46 years, neuropsychological assessment was normal. Neurologic examination revealed discrete generalized choreatic movements and slightly increased muscle tone of the left arm. Cerebral MRI showed no basal ganglia abnormalities. Mutation analysis of the *GCH1* gene was negative (H. Ichinose, Fujita Health University, Toyoake, Japan). Due to the minor extrapyramidal symptoms, the

daily L-dopa/benserazide dosage was increased to 250/62.5 mg. Subsequently, muscle tone normalized, and the choreatic movements remitted, which were therefore interpreted as a residual symptom of the DRD rather than L-dopa-induced motor fluctuations. At the age of 53 years, neuropsychological and neurologic follow-up examination was normal.

Patient 2. The younger brother was born in 1961. His psychomotor development was delayed, probably due to rhesus incompatibility, and he started walking within 24 months. After the age of 3 years, increasing walking problems and dystonia were reported, making him wheelchair-bound within 7 years. Pediatric examination revealed truncal hypotonia, extremity hypertonia, hyperreflexia, and extensor plantar responses. At the age of 12 years, therapy with L-dopa/benserazide 200/50 mg per day enabled him to walk again within 3 weeks. While dystonia and gait completely normalized, episodes of fear and restlessness occurred. Augmentation of the L-dopa/benserazide dosage to 400/100 mg deteriorated the panic disorder, and the medication was reduced to 300/75 mg. At the age of 26 years, neuropsychological assessment demonstrated mild cognitive impairment, probably a consequence of the infantile rhesus incompatibility. Neurologic examination revealed moderate gait problems. Because the panic disorder aggravated, he was hospitalized at the age of 41 years. Neuropsychological assessment and neurologic examination were unchanged. Cerebral MRI was normal (figure). There was no direct temporal relationship between L-dopa intake and the panic attacks. As the dystonia-related immobility was a traumatic experience for him, he refused to reduce the L-dopa medication. At the age of 42 years, however, he stopped the L-dopa medication on his own, and the panic attacks ceased within few days. Concomitantly, he became unable to move, and was transferred to our department. Neurologic examination revealed inability to stand or walk, bradykinesia, generalized dystonia and increased muscle tone, brisk tendon reflexes, and extensor plantar responses. After resumption of the L-dopa/benserazide therapy with 300/75 mg per day, muscle tone gradually decreased, and the neurologic examination normalized within 1 week. Therefore, the extensor plantar responses were interpreted as “striatal toes.” Concomitantly, the panic attacks recurred. Because they did not cease under a therapy of citalopram and lorazepam, and lower L-dopa doses provoked dystonia again, he was transferred to a psychiatric ward for further treatment.

Biochemical analysis. Determination of CSF biogenic amine metabolites was performed as previously described in Patient 2 (table).⁸ The CSF 3OMD level was elevated due to the L-dopa

From the Department of Neurology (Drs. Schiller and Jung), University Hospital Zürich; Laboratory of Pediatrics and Neurology (Drs. Wevers and Steenbergen), University Medical Center, Nijmegen, The Netherlands; and Division of Clinical Chemistry and Biochemistry (Dr. Blau), University Children's Hospital, Zürich, Switzerland.

Received March 26, 2004. Accepted in final form June 2, 2004.

Address correspondence and reprint requests to Dr. Hans H. Jung, Department of Neurology, University Hospital Zürich, Frauenklinikstrasse 26, 8091 Zürich, Switzerland; e-mail: hans.jung@usz.ch

1524 Copyright © 2004 by AAN Enterprises, Inc.

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

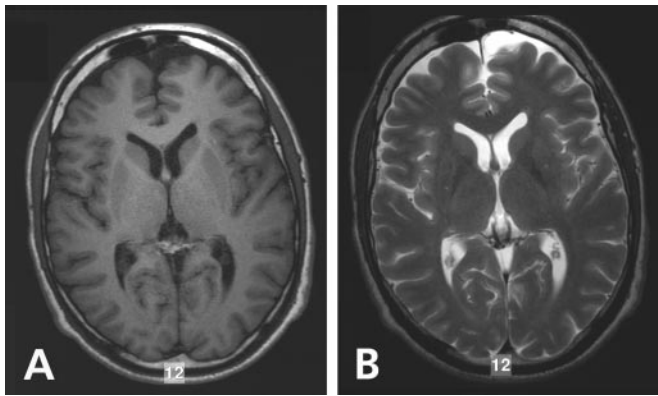


Figure. Cerebral MRI of Patient 2 at the age of 41 years. (A) T1-weighted imaging and (B) T2-weighted imaging does not demonstrate atrophy or pathologic signal alterations in the basal ganglia, cortex, and white matter.

therapy. Significant reductions of the CSF HVA level and the HVA/5HIAA ratio suggested a TH deficiency.

Molecular genetic analysis. To confirm the enzymatic defect, direct sequencing of the *TH* gene was performed as previously described.⁵ A compound heterozygous point mutation was found in both brothers (1127C>T in exon 10, 1493A>G in exon 14). The mother was heterozygous for the 1493A>G mutation. The 1127C>T mutation exchanges an alanine by a valine (A376V), and the 1493A>G mutation exchanges an aspartate by a glycine (D498G). The D498G mutation was already reported in a TH patient in combination with a single nucleotide deletion (296delT), and was not present in a large series of healthy controls.⁹ We did not detect the A376V mutation in 110 healthy alleles by restriction enzyme analysis using BstU I (data not shown).

Discussion. The diagnosis of TH deficiency was established on the basis of the clinical features, CSF biochemical findings, and the presence of a compound heterozygous mutation in the *TH* gene. L-Dopa therapy led to remission of the generalized dystonia-parkinsonism, and a complete treatment response was maintained for over 35 years. Although the L-dopa therapy was delayed up to 20 years after disease onset, there was no evidence for a major cognitive or neurologic impairment as a consequence of the long-term infantile catecholamine deficit. L-Dopa-related disabling panic attacks were observed in one sibling. Because no biochemical evaluations in the pretreatment phase were available to search for possible metabolic differences between the

brothers, the reason for the marked intrafamilial phenotypic variability remains unclear.

TH deficiency usually manifests within the first 3 years of life.^{3-6,9} Untreated TH deficiency causes gradually progressive dystonia-parkinsonism, finally leading to immobilization and contractures.^{4,6,9} Treatment responses to L-dopa are variable. Three patients had favorable treatment responses for almost 30 years without decreasing efficacy.^{4,5} Some patients had favorable treatment responses over shorter follow-up periods.^{3,9} However, several patients had progressive dystonia, parkinsonism, gait ataxia, and cognitive alterations despite sufficient L-dopa therapy.⁶ Although long-term follow-up is lacking in many patients, available data indicate that motor fluctuations do not represent a major problem of the L-dopa therapy.⁵⁻⁷ To our knowledge, L-dopa dependent psychiatric symptoms were not observed in TH deficiency to date.

Based on these clinical observations, two different TH deficiency phenotypes were proposed: 1) DRD and 2) infantile dystonia-parkinsonism with motor delay.⁷ In addition, heterozygous mutation carriers may exhibit exercise-induced stiffness responding to L-dopa therapy.⁹ The phenotypic diversity has been assigned to the degree of residual TH enzymatic activity.^{6,7} This is supported by the fact that patients with a severe TH deficiency phenotype had very low or undetectable HVA CSF levels.⁶

Molecular analysis revealed a compound heterozygous mutation in the *TH* gene. The A376V mutation was observed for the first time. The D498G mutation was reported in another patient in combination with a single nucleotide deletion (296delT).⁹ Available data support the pathogenic importance of the mutations. Both mutations are absent in large series of healthy individuals.⁹ The alanine at nucleotide position 376 (A376) belongs to a highly conserved stretch of 25 amino acids (LGHVPLADRTFAQFSQDI-GLASLG). The conservation rate of this stretch ranges between 88% and 100% in 12 species, and the A376 is conserved in all of them. On protein level, the A376V mutation is predicted to change the alpha-helix and beta-sheet structure between the amino acids 365 and 375. The D498G mutation affects a highly conserved amino acid residue in the tetramerization domain suggesting a significant influence on TH oligomerization.⁹ Various other homozygous and compound heterozygous point mutations were identified in the *TH* gene.^{3,5-7,9} Most disease causing mutations were missense mutations. Only two single base deletions leading to frameshift and a premature termination of the translation were described.⁹ Patients with compound heterozygous mutations tended to have a milder TH deficiency phenotype.^{5,9} Further conclusions about genotype-phenotype correlations, however, remain speculative because of sparse clinical data and lack of long-term follow-up in many patients.

One of our patients had disabling L-dopa-related panic attacks. Although affective symptoms are not generally observed in DRD patients, some patients with *GCH1* deficiency developed sleep disorders, de-

Table Determination of CSF metabolites

Metabolite	Patient 2	Normal range
5-Hydroxyindolacetic acid (5HIAA)	146	66–141
5-Methyltetrahydrofolic acid (5MTHF)	47.0	41–117
Neopterin (Neo)	16.0	9–20
Biopterin (Bio)	14.2	10–30
L-Dopa	16.3	<25
3-O-methyl-Dopa (3OMD)	886	<50
Homovanillic acid (HVA)	66	115–488
HVA/5HIAA ratio	0.45	1.5–3.5

Values are nmol/L.

pression, anxiety, and panic disorders, possibly relating to the serotonin deficiency.^{1,2,7} Patients with idiopathic Parkinson disease, the prototype of a dopamine deficit disorder, may develop panic disorders and generalized anxiety disorders.¹⁰ It remains uncertain, however, if these psychiatric symptoms are caused by the psychological reaction to the illness, disease-related neurochemical changes, or the dopaminergic drugs. In contrast, patients with TH deficiency had no increased frequency of psychiatric symptoms.^{6,7} Therefore, the panic disorder in our patient might represent a direct dopaminergic effect of the L-dopa therapy. As his brother had no adverse effects of the medication, and L-dopa-related panic attacks were not reported from other patients with TH deficiency, an individual cofactor has to be postulated.

References

1. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. *Adv Neurol* 1976;14:215–233.
2. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nat Genet* 1994;8:236–242.
3. Ludecke B, Dworniczak B, Bartholome K. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. *Hum Genet* 1995;95:123–125.
4. Castaigne P, Rondot P, Ribadeau-Dumas JL, Said G. Affection extrapyramidale évoluant chez deux jeunes frères: effets remarquables du traitement par la L-dopa. *Rev Neurol (Paris)* 1971;124:162–166.
5. Swaans RJ, Rondot P, Renier WO, van den Heuvel LP, Steenbergen-Spanjers GC, Wevers RA. Four novel mutations in the tyrosine hydroxylase gene in patients with infantile parkinsonism. *Ann Hum Genet* 2000;64:25–31.
6. Hoffmann GF, Assmann B, Brautigam C, et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. *Ann Neurol* 2003;54(Suppl 6):S56–S65.
7. Furukawa Y. Update on dopa-responsive dystonia: locus heterogeneity and biochemical features. *Adv Neurol* 2004;94:127–138.
8. Blau N, Bonafe L, Thony B. Tetrahydrobiopterin deficiencies without hyperphenylalaninemia: diagnosis and genetics of dopa-responsive dystonia and sepiapterin reductase deficiency. *Mol Genet Metab* 2001;74:172–185.
9. Furukawa Y, Graf WD, Wong H, Shimadzu M, Kish SJ. Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations. *Neurology* 2001;56:260–263.
10. Quinn NP. Classification of fluctuations in patients with Parkinson's disease. *Neurology* 1998;51(Suppl 2):S25–S29.