

injected and the cannula flushed with 1 ml saline. The cannula was then removed and control scans carried out (Fig. 1D).

Discussion

The patient reported here presented with severe anterocollis and mild torticollis to the right. Oral medication had not been successful, and even high-dose BT injections, the treatment of choice in CD, into both sternocleidomastoid muscles had not shown sufficient improvement. Clinical examination revealed the involvement of other head flexors, the hitherto untreated prevertebral muscles, which was the reason for the therapeutic failure. Due to their difficult anatomical position, we decided in favor of a CT-controlled injection technique. BT injection into the right longus colli muscle in combination with injections into both sternocleidomastoid muscles, which were carried out in the traditional way, led to marked improvement of the patient's symptoms.

We conclude that treatment of anterocollis as a particular type of cervical dystonia may be difficult. Simple BT injections into both sternocleidomastoid muscles may be limited by dysphagia. Furthermore, additional involvement of the deep head flexors such as the longus colli or longus capitis muscle could also explain the therapeutic failure. To control correct positioning of the needle during the injection into these muscles, either electromyography (EMG) or CT is required; both techniques necessitate the patient's cooperation. EMG monitoring is less time-consuming, but EMG itself probably does not guarantee placement into the correct muscle (only that the needle tip is in a muscle). Furthermore, it may be complicated by injuries to the adjacent vertebral vessels. This risk can be reduced by ultrasound guidance. Alternatively, the risk of injuring surrounding structures when injecting the deep prevertebral muscles may be minimized by CT assistance, which gives an exact picture of the anatomical structures. Potential drawbacks, however, are X-ray exposure and allergic contrast agent reactions associated with CT monitoring.

In conclusion, treatment of anterocollis has to be decided on an individual basis. In case of insufficient improvement or limiting side effects after chemodenervation of both sternocleidomastoid muscles, controlled injections of the prevertebral muscles as described above should be considered.

References

- Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. *Brain* 1998;121:1195–1212.
- Adler CH, Kumar R. Pharmacological and surgical options for the treatment of cervical dystonia. *Neurology* 2000;55(Suppl.):9–14.
- Tsui JK, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;2:245–247.
- Jankovic J, Schwartz K. Response and immunoresistance to botulinum toxin injections. *Neurology* 1995;45:1743–1746.
- Kessler KR, Skutta M, Benecke R. Long-term treatment of cervical dystonia with botulinum toxin A: efficacy, safety, and antibody frequency. German Dystonia Study Group. *J Neurol* 1999;246:265–274.
- Ruiz PJ, Bernardos VS. Intramuscular phenol injection for severe cervical dystonia. *J Neurol* 2000;247:146–147.
- Massey JM. Treatment of spasmodic torticollis with intramuscular phenol injection. *J Neurol Neurosurg Psychiatry* 1995;30:258–259.
- Münchau A, Palmer JD, Dressler E, et al. Prospective study of selective peripheral denervation of botulinum toxin resistant patients with cervical dystonia. *Brain* 2001;124:769–783.
- Xing Kang D. Selective resection and denervation of cervical muscles in the treatment of spasmodic torticollis: results in 60 cases. *Neurosurgery* 1981;8:680–688.
- Jho HD, Jannetta PJ. Microvascular decompression for spasmodic torticollis. *Acta Neurochir (Wien)* 1995;134:21–26.
- Ford B, Louis ED, Greene P, Fahn S. Outcome of selective ramisectomy for botulinum toxin resistant torticollis. *J Neurol Neurosurg Psychiatry* 1998;65:472–478.
- Vitek JL. Surgery for dystonia. *Neurosurg Clin N Am* 1998;9:345–366.
- Krauss JK, Pohle T, Weber S, et al. Bilateral stimulation of globus pallidus internus for treatment of cervical dystonia. *Lancet* 1999;354:837–838.
- Consky ES, Lang AE. Clinical assessment of patients with cervical dystonia. In: Jankovic J, Hallett M, editors. *Therapy with botulinum toxin*. New York: Marcel Dekker; 1994. p 211–223.

Arg(184)His Mutant GTP Cyclohydrolase I, Causing Recessive Hyperphenylalaninemia, Is Responsible for Dopa-Responsive Dystonia With Parkinsonism: A Case Report

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Abstract: We describe a 54-year-old man with dominant adult-onset dopa-responsive dystonia (DRD) with parkinsonism caused by an Arg184His mutation in guanosine 5'-triphosphate cyclohydrolase I (GCH-I). This is the first mutation in the GCH-I gene that has been proven to be responsible for both recessive and dominant phenotypes. © 2003 Movement Disorder Society

Key words: dopa-responsive dystonia with parkinsonism; GTP cyclohydrolase I gene; Arg(184)His mutant; adult-onset; hyperphenylalaninemia

A videotape accompanies this article.

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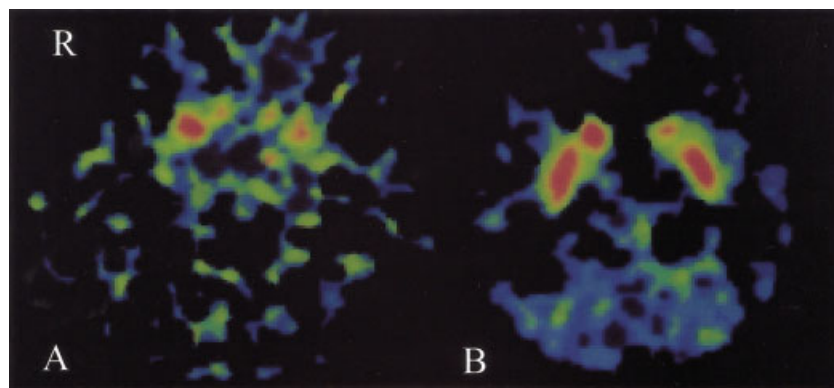


FIG. 1. PET finding. ^{18}F -fluorodopa uptake was decreased in both the caudate nucleus and putamen in the patient (A) compared to age-matched, normal control subjects (B).

Dopa-responsive dystonia (DRD) is a childhood or adolescent onset hereditary dystonia that responds well to levodopa (L-dopa) with few complications, such as L-dopa-induced dyskinesia. Most patients of DRD, inherited as an autosomal dominant trait with reduced penetrance (~30%), have been shown to be associated with mutations in the guanosine 5'-triphosphate cyclohydrolase I (GCH-I) gene.¹ Because the gene products are related to tyrosine hydroxylation, impaired dopamine production seems to be responsible for DRD. Although dopamine is depleted in nigral cells, the nigral dopaminergic cells are spared and dopaminergic transmission is potentially intact in DRD.² Homozygous mutations of GCH-I, however, have been associated with hyperphenylalaninemia, characterized by neonatal onset, severe multiple neurological dysfunctions possibly due to catecholamine and serotonin deficiency. Because no cases with DRD have been reported among the pedigrees of hyperphenylalaninemia and no reported mutations in the GCH-I gene are shared by the two phenotypes, it has been suggested that there may be possible qualitative differences in the mutant gene products between the two phenotypes.

We report on a patient with adult-onset dystonia with a missense GCH-I mutation, which was reported previously to be responsible for the GCH-I deficiency with hyperphenylalaninemia.³ This patient showed reduced ^{18}F -fluorodopa (^{18}F -dopa) uptake in the striatum, which suggested impaired dopaminergic transmission in a nigrostriatal pathway.

Case Report

A 54-year-old Japanese man first noticed postural and fine tremor in the left hand and motor difficulty due to dystonia with mild bradykinesia at the age of 39 years. He gradually developed dystonic posture, which spread from the right to the left side within several years. From his middle 40s, he had experienced difficulty in walking due mainly to dystonia. His past medical history and family history revealed no other neurological disease. He had dystonic posture in all four limbs with right side dominance, in addition to moderate lead pipe rigidity, akinesia, and postural instability (see Video). After L-dopa decarboxylase inhibitor (DCI) administration these symptoms improved markedly, except for mild rigidity in his four extremities (see Video). The motor score of the Unified Parkinson's Disease Rating Score (UPDRS) was 44 without treatment and 6 with L-dopa/DCI. At first, a single-dose of L-dopa/DCI was effective for 5 to 6 hours, but after 11 years of treatment, this dose lasted for only a couple of hours. The dose of

L-dopa/DCI necessary to allow usual daily activities increased gradually from 100 to 600 mg/day. His main symptom since onset had been dystonia, before the introduction of L-dopa supplementations. Concomitant parkinsonian symptoms such as bradykinesia were present, but to only a mild degree. The dystonia consistently has shown a good response to L-dopa for over 15 years, and during the *on* status, he has been quite free from the symptoms. In the early stage of the disease, he did not show the on-off phenomenon or drug-induced dyskinesia, but later suffered from both unremarkable complications. Neuropsychological testing showed a total IQ of 75, which was composed of a performance IQ of 64 and a verbal IQ of 88 without impaired memory functions. Although the examination was undertaken during *on* status, the patient could not keep a good condition during the examination because of motor and non-motor fluctuations. He showed neither sensory disturbances nor cerebellar signs, deep tendon reflexes in the four extremities were brisk, and no pathological reflexes were observed.

Routine blood examinations, ceruloplasmin and copper in serum, copper in urine, and plasma phenylalanine were normal. The levels of total biopterin (4.1 pmol/ml) and neopterin (2.8 pmol/ml) in the cerebrospinal fluid (CSF) were extraordinary low compared with those in normal control CSF (biopterin, 26.4 ± 8.5 pmol/ml; neopterin, 22.1 ± 7.0 pmol/ml).⁴ The GCH-I activity (10.0 pmol/hr/mg protein) in phytohemagglutinin (PHA)-stimulated mononuclear cells¹ was also much lower than that in normal controls (39.0 ± 9.2 pmol/hr/mg protein). Brain magnetic resonance imaging (MRI) was normal and ^{123}I -IMP SPECT showed hyperperfusion in the bilateral basal ganglia. Before the positron emission tomography (PET) study (Fig. 1A), dopaminergic treatment was suspended for 18 hours.⁵ The influx rate constant (Ki) of ^{18}F -dopa into selected regions⁵ was reduced in the caudate nucleus (0.0075) and in the putamen (0.0045) compared with 8 age-matched normal controls (caudate nucleus, 0.0129 ± 0.0029 ; putamen, 0.0114 ± 0.0021) (Fig. 1B). Genomic DNA was extracted from peripheral blood leukocytes. All six exons, including the splicing junction and promoter region, were amplified using polymerase chain reaction (PCR) and sequenced directly with an automated DNA sequencer.^{1,6} We found a single base change (G-to-A transition) in exon 5 causing an amino acid substitution of Arg184His (Fig. 2A). Because surveys of all coding sequences identified no other mutations or polymorphisms, the mutation was not compound heterozygous. This mutation created a new

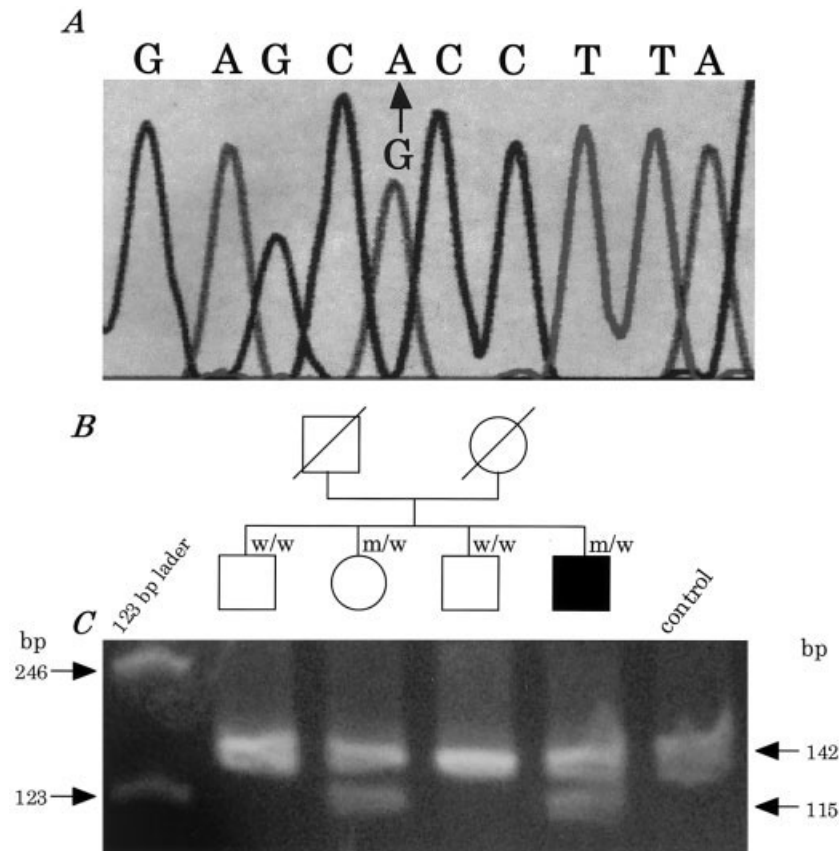


FIG. 2. **A:** Analysis of the GCH-I gene. Sequence analysis showed a single base change (G-to-A transition) in exon 5 causing an amino acid substitution of Arg184→His. **B:** Pedigree of a DRD family with mutation in the GCH-I gene. The affected proband is represented by a solid symbol, and unaffected family members by open symbols. **C:** *Bsp*I restriction site analysis of genomic DNA. The mutation creates a new *Bsp*I cleavage site, and the *Bsp*I digestion of the PCR product generates 115- and 142-base pair bands in the mutant allele.

*Bsp*I cleavage site in the mutant allele (Fig. 2C). The patient was heterozygous for the mutation and this genotype was shared by an asymptomatic sibling (Fig. 2B). Gene analyses of 100 normal control subjects and 100 idiopathic Parkinson's disease (PD) patients failed to demonstrate this mutation and there were no mutations in the coding region of the parkin gene.⁷ The study procedures were approved by the institutional ethical committee.

Discussion

The clinical symptoms of this patient can be summarized as DRD with parkinsonism. Some of his symptoms are not typical of childhood- or adolescent-onset DRD and there may be a possibility of a chance association between the observed phenotype and the mutation in GCH-I. His main symptom, however, has been dystonia since onset of the disease. Concomitant parkinsonian symptoms such as bradykinesia were present, but to only a mild degree. After several years from the onset, motor fluctuations were observed, but their severities were much milder than were those in the authentic PD. His dystonia has shown a consistently good response to L-dopa for over 15 years, and, during the *on* status, he has been quite free from the symptoms. Moreover, laboratory data demonstrated low (below 20% of normal values) levels of biopterin and neopterin in the CSF and low GCH-I activity in peripheral lymphocytes. Given these features, we diagnosed his condition as DRD.^{1,8,9} Interestingly, the GCH-I mutation identified in this patient had been reported previously to cause hyperphenylalaninemia, another

recessive form of this gene phenotype. Null GCH-I activity is thought to be lethal, and in fact, little enzymatic activity was detected for protein products derived from mutated GCH-I genes, such as the Arg184His mutation that causes recessive hyperphenylalaninemia. In dominant DRD, decreased GCH-I activity is usually less than 20% of normal values despite the presence of a normal allele. In co-transfection experiments, the pathomechanisms derived from the mutated GCH-I proteins between these two phenotypes were different. Recently, several reports have suggested dominant-negative effects of mutated gene products corresponding to the DRD.^{10,11} The peculiar pattern detected by gel filtration chromatography,¹² however, suggests that this Arg184His mutated protein has a unique conformation and may not be able to interact easily with the normal GCH-I protein. Therefore, the dominant negative mechanisms are not likely to play a role in development of the DRD phenotype in this patient. Combined with the low (<30%) penetrance and the female predominance in dominant DRD, this case suggests that not only defects in the GCH-I gene but also other factors may contribute to the development of this phenotype.

The PET study revealed that ¹⁸F-fluorodopa uptake was decreased significantly in both the caudate nucleus and the putamen, although PET studies in childhood or adolescent onset DRD usually demonstrated normal uptake of ¹⁸F-fluorodopa in the brain.¹³ The Ki ratio of the caudate to the putamen in this patient was 1.66, similar to the values for adult-onset dystonia-parkinsonism (DYS-P) reported by Turjanski and col-

leagues.¹³ Although their patients were not analyzed genetically, the clinical features of their DYS-P patients are similar to those of this patient. The development of parkinsonian features in adulthood-onset DRD may be related to age-dependent differences in the function of the basal ganglia-thalamocortical motor loop.¹⁴ Alternatively, the chronic decrease in the GCH-I activity may result in not only dopamine depletion in nigral cells, but also in impaired synaptic functions in the nigrostriatal pathways. Levels of tyrosine hydroxylase have been reported to be reduced in the striatum, with the loss more pronounced in the putamen than in the caudate.^{15,16} It has also been suggested that dopamine transporters are decreased in the putamen, and these data might reflect a putative regression of nerve terminals derived from nigral dopaminergic neurons, especially in the putamen.^{15,16} In fact, some DRD patients with the GCH-I mutation showed parkinsonism with motor fluctuations, which seemed to be caused by the nigrostriatal denervation in DRD.¹⁷ It is suggested that a synaptic dysfunction in the striatum may play a role in the development of the parkinsonian features in adult-onset DRD.^{15,18} Further analyses in genetically proven DRD will be informative not only for elucidating the pathomechanisms of DRD, but also for promoting our understanding of physiological roles of GCH-I in dopaminergic neurons during development and aging.

Legends to the Video

Segment 1. The patient without L-dopa/DCI supplementation showed bradykinesia and dystonic posture in the four extremities with right-side dominance, such as equinovarus of the right leg. He had difficulty in walking because of dystonic postures.

Segment 2. The patient L-dopa/DCI did not show bradykinesia or dystonic posture.

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References

1. 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.
2. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. *Adv Neurol* 1976;14:215–233.
3. Ichinose H, Ohye T, Matsuda Y, et al. Characterization of mouse and human GTP cyclohydrolase I genes. Mutations in patients with GTP cyclohydrolase I deficiency. *J Biol Chem* 1995;270:10062–10071.
4. Fujishiro K, Hagihara M, Takahashi A, Nagatsu T. Concentrations of neopterin and biopterin in the cerebrospinal fluid of patients with Parkinson's disease. *Biochem Med Metab Biol* 1990;44:97–100.
5. Hu XS, Okamura N, Arai H, et al. 18F-fluorodopa PET study of striatal dopamine uptake in the diagnosis of dementia with Lewy bodies. *Neurology* 2000;55:1575–1577.
6. Bandmann O, Valente EM, Holmans P, et al. Dopa-responsive dystonia: a clinical and molecular genetic study. *Ann Neurol* 1998;44:649–656.
7. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392:605–608.
8. Ichinose H, Suzuki T, Inagaki H, Ohye T, Nagatsu T. Molecular genetics of dopa-responsive dystonia. *Biol Chem* 1999;380:1355–1364.
9. Furukawa Y, Shimadzu M, Rajput AH, et al. GTP-cyclohydrolase I gene mutations in hereditary progressive and dopa-responsive dystonia. *Ann Neurol* 1996;39:609–617.
10. Hirano M, Yanagihara T, Ueno S. Dominant negative effect of GTP cyclohydrolase I mutations in dopa-responsive hereditary progressive dystonia. *Ann Neurol* 1998;44:365–371.
11. Hwu WL, Chiou YW, Lai SY, Lee YM. Dopa-responsive dystonia is induced by a dominant-negative mechanism. *Ann Neurol* 2000;48:609–613.
12. Suzuki T, Ohye T, Inagaki H, Nagatsu T, Ichinose H. Characterization of wild-type and mutants of recombinant human GTP cyclohydrolase I: relationship to etiology of dopa-responsive dystonia. *J Neurochem* 1999;73:2510–2516.
13. Turjanski N, Bhatia K, Burn DJ, Sawle GV, Marsden CD, Brooks DJ. Comparison of striatal 18F-dopa uptake in adult-onset dystonia-parkinsonism, Parkinson's disease, and dopa-responsive dystonia. *Neurology* 1993;43:1563–1568.
14. Segawa M, Nomura Y. Hereditary progressive dystonia with marked diurnal fluctuation. Pathophysiological importance of the age of onset. *Adv Neurol* 1993;60:568–576.
15. Furukawa Y, Nygaard TG, Gutlich M, et al. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. *Neurology* 1999;53:1032–1041.
16. Rajput AH, Gibb WR, Zhong XH, Shannak KS, Kish S, Chang LG, Hornykiewicz O. Dopa-responsive dystonia: pathological and biochemical observations in a case. *Ann Neurol* 1994;35:396–402.
17. Tassin J, Durr A, Bonnet AM, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? *Brain* 2000;123:1112–1121.
18. Steinberger D, Weber Y, Korinthenberg R, Deuschl G, Benecke R, Martini J, Muller U. High penetrance and pronounced variation in expressivity of GCH1 mutations in five families with dopa-responsive dystonia. *Ann Neurol* 1998;43:634–639.

SCA2 Presenting as Levodopa-Responsive Parkinsonism in a Young Patient From the United Kingdom: A Case Report

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Abstract: We report on a young woman from the United Kingdom with L-dopa-responsive parkinsonism with a trinucleotide repeat expansion in her spinocerebellar ataxia 2

A videotape accompanies this article.

This article contains supplementary video clips, available online at <http://www.interscience.wiley.com/jpages/0885-3185/suppmat>

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