FEATURED ARTICLE

Levodopa-Induced Dyskinesias in Tyrosine Hydroxylase Deficiency

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ABSTRACT: The objective of this study was to characterize levodopa (L-dopa)–induced dyskinesias in patients with tyrosine hydroxylase deficiency. Clinical observation was carried out on 6 patients who were diagnosed with tyrosine hydroxylase deficiency and were treated with escalating doses of L-dopa. All 6 patients showed L-dopa-induced dyskinesias of variable intensity early in the course of treatment and regardless of the age of initiation. L-Dopa–induced dyskinesias were precipitated by increases in the dose of L-dopa and also by febrile illnesses and stress. They caused dysfunction and distress in 2 patients. The dyskinesias were improved by decreasing the L-dopa dose or by slowing its titration upward. Increasing the dose frequency was helpful in 2 patients, and introducing amantadine was helpful in another 2 patients. L-Dopa–induced dyskinesias are a common phenomenon in tyrosine hydroxylase deficiency. The current observations show that L-dopa–induced dyskinesias are frequent in a dopamine-deficient state in the absence of nigrostriatal degeneration. Although L-dopa–induced dyskinesias in tyrosine hydroxylase deficiency are phenomenologically similar to those that occur in Parkinson's disease, they are different in a number of other respects, suggesting intrinsic differences in the pathophysiologic basis of L-dopa–induced dyskinesias in the 2 conditions. © 2013 *Movement* Disorder Society

Key Words: levodopa; dyskinesias; tyrosine hydroxylase deficiency; chorea

Tyrosine hydroxylase (TH) deficiency is an autosomal recessive disorder that leads to a deficiency in the production of dopamine, epinephrine, and norepinephrine.[1] Patients present with developmental delay, infantile parkinsonism, oculogyric crises (OGCs), and features of autonomic dysfunction.

The treatment of choice for TH deficiency is levodopa (L-dopa); alternatively, patients also are treated with other dopaminergic drugs, mainly dopamine agonists and monoamine oxidase inhibitors.[2,3] On the basis of a large series of patients, 2 clinical phenotypes of TH deficiency were described: a progressive, hypokinetic-rigid syndrome with dystonia and onset during infancy or childhood (type A), and a complex encephalopathy with onset in the neonatal period or early infancy (type B). Although type A patients show good tolerance to L-dopa and an excellent response of motor function, type B patients show poor tolerance to L-dopa and worse motor outcome.[2]

L-Dopa–induced dyskinesias (LIDs) are classically seen in Parkinson's disease patients, and it is believed that they are related to the underlying neuronal degeneration in combination with L-dopa exposure.[4] LIDs also may occur in patients with TH deficiency and in other defects of biogenic amine synthesis; in some patients, the dyskinesia may be severe enough to impede treatment.[1] Despite the increasing awareness and diagnosis of biogenic amine disorders in the last

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decade, LIDs in this group of diseases have not been well characterized. To better understand the phenomenology and gain insights into the underlying mechanisms of LIDs in biogenic amine disorders, we describe LIDs in 6 patients with TH deficiency.

Patients and Methods

The main clinical manifestations of each patient are depicted in Table 1. Patients 1, 2, and 3 have been described previously.[5]

The clinical presentation of all of our patients was within the known spectrum of TH deficiency and corresponds to the type B phenotype described by Willensem et al.[3] All patients presented with infantile parkinsonism, failure to make motor acquisitions, and OGCs. Their OGCs were variable in severity. Mild OGCs consisted of episodes of upgaze deviation of a few seconds in duration that recurred multiple times over minutes or several hours and were not associated with distress or abnormal posturing of the limbs or trunk. Severe OGCs consisted of episodes of sustained upgaze deviation associated with distress and limb, cervical, and trunk dystonia with a duration of minutes to several hours.

All patients were diagnosed based on measurements of biogenic amine metabolites in spinal fluid, indicating a profound reduction of homovanillic acid levels with normal serotonin metabolites.[5] Sequencing analysis of the *TH* gene in patients 1 through 5 revealed a previously reported homozygous pathogenic mutation in exon 6 (c.707T > C), causing a substitution of leucine for proline at residue 236 (p.Leu236Pro).[6] Molecular analysis could not be performed on patient 6 because she was lost to follow-up.

Patients 1 through 5 were treated with the commercially available formulation of L-dopa/carbidopa (1.00:0.25). The starting dose was 0.5 to 1.0 $mg \cdot kg^{-1} \cdot d^{-1}$. When the patients developed dyskinesias, L-dopa was decreased to the previously tolerated dose, maintained at the same dose, or the dose was increased slowly. The rate of increase was individualized according to the presence of and tolerance to dyskinesias. The fastest tolerated rate of increase was 1 $mg \cdot kg^{-1}$ d^{-1} each month for 3 consecutive months (patient 2), and the slowest was 0.1 $mg \cdot kg^{-1} \cdot d^{-1}$ over 17 months (patient 1). The number of daily doses varied among the patients, according to their daily activities and tolerance, ranging from 3 to 5 times a day. Regarding the timing of the appearance of dyskinesias in relation to L-dopa administration, their parents often reported them within 1 hour of administration and less often before the administration of the next dose.

The management of patient 6 differed. At the age of 23 months, she was started on L-dopa at 0.1 mg/kg for 1 day, followed by 0.6 $mg \cdot kg^{-1} \cdot d^{-1}$ for 2 days, and then continued on 0.8 $mg \cdot kg^{-1} \cdot d^{-1}$. Within the first few days of treatment, she developed prominent dyskinesias of all limbs that were interpreted by the parents as myoclonic seizures. They discontinued the therapy, and the patient was lost to follow-up. At 10 years of age, the parents were contacted, and a new L-dopa regimen of 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ was recommended. The parents did not report dyskinesias; however, the patient was once again lost to follow-up.

The dyskinesias in all of our patients consisted of chorea of the limbs, face, and trunk (Video 1). In patients 1, 3, and 5, jaw-opening dystonia was noted early in the course of treatment. Ballistic movements were reported in patient 4. Detailed clinical descriptions of the appearance and course of LIDs in 3 representative patients are presented as the Supplementary Material.

Gross Motor Function Measure

The 66-item version of the Gross Motor Function Measure (GMFM)[7] was performed in patients 1 through 5. The GMFM evaluates a child's gross motor skills in 5 different dimensions: lying and rolling; sitting; crawling and kneeling; standing; and walking, running, and jumping. The sum of all the items gives the percentage performance achieved by the patient.[7] The clinician performing the measurements (D.S.) was blinded to the dose of L-dopa. All patients showed progressive acquisition of motor milestones with gradual increases in the dose of L-dopa. The progress of their GMFM measurements is depicted in Figure 1. This study was performed in accordance with the Helsinki declaration. Informed consent was obtained from the patients' parents.

Discussion

LIDs are movement disorders, classically described in Parkinson's disease, that are precipitated by L-dopa and other dopaminergic drugs. They show variable phenomenology, including dystonia and choreic movements, and they may occur at different time points of the L-dopa drug cycle.[8] The incidence of LIDs in Parkinson's patients is 30% and 90% after 4 to 6 years and 9 years of treatment, respectively.[8,9]

Although they are characteristic of Parkinson's disease, LIDs also have been reported in inherited defects of dopamine synthesis.[1] Although LIDs in Parkinson's disease are related to neurodegeneration and striatal denervation,[4] this is not the case in inherited defects of dopamine synthesis. The lack of a neurodegenerative pathohpysiological process in TH-deficient patients is supported by the nonprogressive nature of

TABLE 1. Main clinical features of the 6 tyrosine hydroxylase-deficient patients

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at onset/at diagnosis, mo	3/24	5/5	3/5	4/8 y	2/6	3/20
Developmental delay/loss of previously acquired head control[a]	+/+	+/+	+/+	+/−	+/−	+/+
Hypotonia	+	+	+	+	+	+
Minimal spontaneous movements	+	+	+	+	+	+
Dystonia[b]	+	+	+	+	+	+
Tremor	+	+	+	+	+	+
OGCs	Severe	Mild	Severe	Mild	Mild	Severe
Antiepileptic treatment[c]	Vigabatrin, levetiracetam	None	Phenobarbital	None	None	Phenobarbital, valproic acid, vigabatrin, carbamazepine, phenytoin, topiramate
Diurnal fluctuation/sleep benefit	+	−	+	+	+	+
Autonomic dysfunction[d]	+	+	+	+	+	+
Time of LIDs presentation after initiation of treatment, mo	6	10	At first dose	6	First days	23
Type of dyskinesias	Dystonia,[e] chorea	Chorea	Dystonia,[e] chorea	Chorea, ballism	Dystonia,[e] chorea	Chorea
L-dopa dose inducing dyskinesias[f]	2.0	5.0	1.0	3.3	0.5	0.1–0.8
HVA (normal range), nmol/L[g]	50 (344–906)	31 (354–1328)	18.5 (354–1328)	5 (158–596)	18 (344–906)	22 (154–867)
HIAA (normal range), nmol/L	197 (170–490)	270 (217–1142)	235 (217–1142)	192 (87–366)	247 (170–490)	165 (89–367)
HVA/HIAA (normal range)	0.25 (1.11–3.48)	0.11 (1.16–2.4)	0.08 (1.16–2.4)	0.03 (1.5–3.5)	0.07 (1.5–3.5)	0.13 (1.0–3.7)
MHPG (normal range), nmol/L	20 (20–80)	1.6 (30–124)	1.4 (30–124)	0 (13–68)	0 (20–80)	Not available
3OMD (normal range), nmol/L	10 (4–50)	4.6 (20–162)	10 (20–162)	0 (3–64)	7 (4–50)	Not available

[a]Head control was achieved within the first 3 months of life and subsequently lost.
[b]Dystonic movements were observed when the infants were manipulated and stressed.
[c]Antiepileptic treatment was given to patients in whom oculogyric episodes had been interpreted as seizures.
[d]Excessive sweating, increased upper respiratory secretions.
[e]Jaw-opening dystonia.
[f]Values indicate levodopa (L-dopa) dose in $mg \cdot kg^{-1} \cdot d^{-1}$.
[g]The normal range of metabolite concentration was age-dependent.[5]
Abbreviations: OGCs: oculogyric crises; LIDS, L-dopa-induced dyskinesias; HVA, homovanillic acid; HIAA, 5-hydroxyindoleacetic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; 3OMD, 3-ortho-methyldopa.

the disorder,[3] and the essentially normal 18-Fluorodopa positron emission tomography scans,[10] ruling out significant nigrostriatal degeneration. In addition, postmortem studies of patients with deficits of guanosine triphosphate cyclohydrolase, the rate limiting enzyme for the synthesis of tetrahydrobiopterin (BH_4), the cofactor of TH, revealed no abnormalities in the substantia nigra or in the basal ganglia.[11] Further support comes from animal model studies in which dopamine-neuron–specific TH knockout mice showed normal innervation of the striatum with no evidence of degeneration.[12]

The occurrence of LIDs in TH deficiency in the absence of nigrostriatal degeneration runs against the dogma that LIDs only occur in the setting of dopaminergic degeneration.[4] Although research progress is leading to the understanding of the pathophysiological basis of LIDs in Parkinson's disease, little is known about LIDs in inherited defects of dopamine synthesis. In the current study, we analyzed the characteristics of LIDs in TH deficiency based on our experience in 6 patients.

All of our patients developed dyskinesias within the first few months of treatment (Table 1); LIDs occurred at variable doses of L-dopa in each patient, ranging from 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ to 5.0 $mg \cdot kg^{-1} \cdot d^{-1}$. We initially managed the dyskinesias by decreasing the L-dopa dose or by slowing the rate of increase of L-dopa, which led to an improvement in the intensity and frequency of dyskinesias in all patients. This strongly suggests that the dyskinesias were related to the administration of L-dopa. The age of our patients at the start of L-dopa therapy ranged from 5 months to 8 years. Despite the limited number of patients, in our experience, LIDs occurred regardless of age at the onset of treatment.

The phenomenology of LIDs in our patients was consistent with chorea, and it involved mainly the face, limbs, and trunk (Video 1). The severity of LIDs was variable among our patients. Attempts to quantify the dyskinesias objectively failed, because they fluctuated and because the parents often did not experience them as a problem. However, LIDs occasionally caused distress and functional disturbance; for example, in patient 3, the initial doses of L-dopa precipitated severe tongue thrusting that impeded feeding; in patient 4, L-dopa also precipitated oral dyskinesias and severe, distressing ballistic movements. In patient 6, dyskinesias were interpreted as myoclonic seizures and led to the discontinuation of L-dopa therapy by the parents.

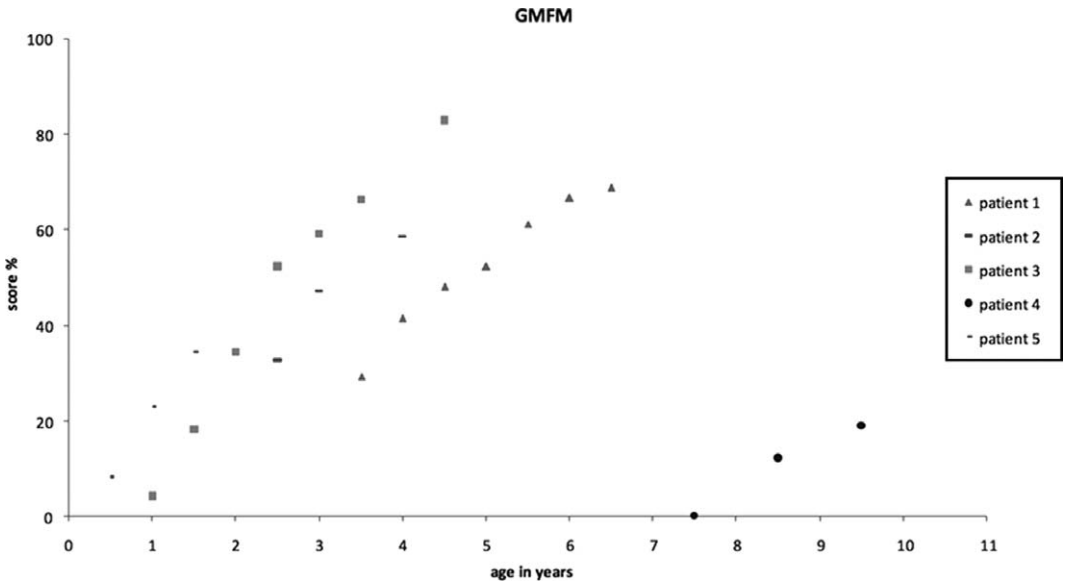

FIG. 1. Progress of gross motor function measure (GMFM) is illustrated in 5 tyrosine hydroxylase (TH)-deficient patients. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Early in the course of L-dopa treatment, 3 patients developed jaw-opening dystonia (Table 1). The pathophysiology of this movement disorder was thought to be different from the LIDs described above. All of our patients failed to make motor acquisitions, as mentioned above; but they gradually acquired motor function after the introduction of L-dopa treatment (Fig. 1). Initially, 3 of our patients (patients 1, 2, and 3) exhibited action dystonia that gradually improved and eventually disappeared. Action dystonia was mainly noted in the limbs, first in the upper limbs and, later, when standing was achieved, in the lower limbs. Thus, it is possible that action dystonia emerged as a default pattern of motor learning in TH deficiency.[13] On the basis of this observation, we believe that jaw-opening dystonia also may represent a default pattern of motor development involving the cranial musculature. A different pathophysiological origin of L-dopa–induced chorea and action dystonia is supported by the fact that, in patients who had developed jaw-opening dystonia, cranial dystonia gradually disappeared, whereas choreic dyskinesias continued. In addition, there was no clear relation between the timing of L-dopa administration and dystonic movements.

LIDs occurred mainly at the expected peak of the L-dopa blood levels after oral administration, although, in some patients (patients 1 and 4), they were also present during an apparent trough. Similar to Parkinson's disease, different forms of dyskinesias (peak dose and diphasic dyskinesias) are probably part of a clinical continuum.[8] In all of our patients with TH deficiency, the main aggravating factor for LIDs was the increase in the L-dopa dose. In addition, in some patients, LIDs worsened in the setting of intercurrent febrile illnesses (patients 1 and 3) and were aggravated by tiredness and overexcitement (patients 1 and 2). In patient 4, a severe episode of dyskinesias occurred with no clear precipitating factor.

The LIDs in our TH-deficient patients evolved over time. They were initially present in the face and tongue and peripherally in the limbs, mainly in the hands (Video 1). They became more generalized when the patients became more mobile and had trunk control. When the patients achieved independent walking, they walked with a dance-like appearance (Video 1). In the more functionally advanced patients, the dyskinesias tended to evolve into fluctuating fidgetiness. In patient 3, the dyskinesias disappeared by the age of 4 years.

We managed LIDs in our patients by decreasing their L-dopa dose or by slowing its rate of increase, as mentioned above. Once the dyskinesias improved, we attempted to further increase the L-dopa dose; however, although L-dopa could be increased steadily in patients 2 and 3, the rate of increase in patients 1 and 4 was very slow and even was interrupted for several months. In patients 3 and 5, increasing the dose frequency to 4 and 5 times a day appeared to help; whereas, in patients 2 and 5, amantadine was introduced, which allowed further increases in the L-dopa dose.

In Parkinson's disease, the earlier occurrence and higher prevalence of LIDs is associated with the severity of the disease, which, in turn, reflects the extent of striatal denervation.[9] All of our patients showed profound parkinsonism, failure to develop any motor milestones, and OGCs of variable severity (Table 1). OGCs are a common feature of inherited metabolic disorders, leading to dopamine deficiency; however, their pathophysiological basis remains unknown. It is

TABLE 2. Levodopa-induced dyskinesias in patients with tyrosine hydroxylase deficiency and Parkinson's disease

Variable	Parkinson's disease	TH deficiency
Incidence	30%–90%	100%
Emergence	Within 4–6 years of treatment	Within the first few days to months of the onset of treatment
Phenomenology	Chorea, dystonia	Chorea, dystonia, ballism
Location	Face, limbs, trunk	Face, limbs, trunk
Severity	Mild to severe	Mild-to-moderate; occasionally severe
Relation to dose	Peak dose, diphasic dyskinesias	Mainly peak dose, possibly also trough
Risk factors	Disease severity, early onset, longer duration of the disease, L-dopa total exposure, female gender, possibly genetic factors	Rapid increase of L-dopa dose, tiredness, excitement, intercurrent infections, concomitant antiepileptic drugs, possibly the severity of oculogyric episodes
Management	Amantadine, continuous dosing	Slow increase rate of dose, increased frequency of dosing, amantadine

Abbreviation: TH, tyrosine hydroxylase.

possible that the severity of OGCs in TH deficiency is an indication of the degree of striatal dopamine deficiency. In our experience, patients with severe OGCs appeared more prone to develop LIDs; however, when we analyzed the doses of L-dopa leading to LIDs in our group of patients, they overlapped, i.e., 0.5 to 5.0 $mg \cdot kg^{-1} \cdot d^{-1}$ in the group with mild OGCs and 0.1 to 2.0 $mg \cdot kg^{-1} \cdot d^{-1}$ in the group with severe OGCs. Unfortunately, the number of patients in our study was limited and the role of OGCs as a potential risk factor for dyskinesias is speculative.

Our patients had variable homovanillic acid levels in their spinal fluid; and, although the number of patients was limited, there was no apparent correlation between their homovanillic acid values and the risk of presenting with LIDs. Genetic or environmental factors also could be involved in the predisposition to develop dyskinesias.

In Table 2, we highlight the main clinical characteristics of LIDs in patients with Parkinson's disease and TH deficiency. Given the phenotypic similarities of LIDs in Parkinson's disease and in TH-deficient patients (Table 2), it is reasonable to consider that they share some common pathophysiological mechanisms. On the basis of animal models, a major determinant of LIDs in Parkinson's disease is an exuberant postsynaptic response to dopamine because of type D2 and D1 dopamine receptor supersensitization after dopamine denervation in the striatum.[9] It is likely that this mechanism of supersensitization also plays a role in TH deficiency in which the striatum has been exposed to minimal dopamine concentrations since early life. However, in TH deficiency, such a mechanism would operate in the absence of denervation.[10–12] In Parkinson's disease, chronic L-dopa treatment in the denervated striatum leads to further D1 receptor "sensitivity enhancing" changes that have been implicated in the increase in the severity of dyskinesias. This mechanism probably does not play a role in TH deficiency, in which the L-dopa dose is gradually increased, and dyskinesias tend to improve and even resolve over time (patient 3).

Another postulated mechanism for the induction of dyskinesias is the excessive excitatory influences of glutamatergic corticostriatal projections on the direct pathway. Blockade of N-methyl-D-aspartic acid (NMDA) receptors by amantadine, which leads to the attenuation of the glutamatergic drive, is probably responsible for the antidyskinetic actions of this drug in Parkinson's disease.[14] The fact that 2 of our patients showed an improvement of their dyskinesias with amantadine suggests that glutamatergic influences also play a role in the induction of dyskinesias in TH deficiency.

TABLE 3. Treatment recommendations in patients with tyrosine hydroxylase deficiency[a]

Variable	Recommendation
Initial L-dopa dose	0.5–1.0 $mg \cdot kg^{-1} \cdot d^{-1}$ divided into 3–6 doses
Increments of L-dopa	Increase L-dopa dose by 0.1–0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ according to tolerance every month
Management when dyskinesias appear	Decrease L-dopa to the previously tolerated dose Postpone further increases of L-dopa dose until the dyskinesias decrease or recede Increase the dose frequency
Initiation of amantadine	When the above measures are insufficient to control the dyskinesias
Amantadine dose	4–6 $mg \cdot kg^{-1} \cdot d^{-1}$
Chronic L-dopa dose	3–20 $mg \cdot kg^{-1} \cdot d^{-1}$ according to tolerance
Introduction of other dopaminergic agents	When L-dopa cannot be tolerated and/or when L-dopa is insufficient to provide a meaningful clinical response

[a]Recommendations are based on our experience and a larger case series.[3]

The nonregulated release and defective clearance of exogenously derived dopamine, which leads to large and intermittent fluctuations in the extracellular levels of dopamine in the brain, have also been implicated in the induction of LIDs in Parkinson's disease. On the basis of this concept, methods of continuous L-dopa delivery have been shown to improve dyskinesias and motor fluctuations in Parkinson's disease.[15] Similarly, in 2 of our TH-deficient patients (patients 3 and 4), improvements in their dyskinesias were noted when dose frequency was increased.

In summary, LIDs represent a common phenomenon in TH deficiency. All of our TH-deficient patients presented with LIDs of variable intensity early in the course of treatment and regardless of the age at which treatment was initiated. LIDs were precipitated by increases in the dose of L-dopa and also by febrile illnesses and stress. Occasionally, they caused dysfunction and distress. Severe OGCs appear to be a risk factor for developing LIDs at lower L-dopa doses. Similarities and differences with LIDs in Parkinson's disease can help us to understand the pathophysiological basis of LIDs in congenital conditions with dopamine deficiency. The treatment recommendations for LIDs in TH-deficient patients are depicted in Table 3.

This report is based on uncontrolled clinical observations, an approach inherent to the rarity of this condition. Functional studies and studies in animal models of TH deficiency and other states of dopamine deficiency are necessary to investigate further the pathophysiological basis of LIDs in these conditions. ■

Legends to the Videos

Video 1. In Patient 1, separate clips show 1) fidgetiness and chorea, 2) motor impersistence when trying to maintain a posture, 3) dance-like gait, 4) moderate chorea affecting the upper limbs and face, and 5) incoordination of fine hand movements. In Patient 5, clips show 1) lingual dyskinesias and 2) oral and facial dyskinesias.

References

1. Pons R, The phenotypic spectrum of paediatric neurotransmitter diseases and infantile parkinsonism. J Inherit Metab Dis 2009;32:321–332.
2. 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.
3. Willemsen MA, Verbeek MM, Kamsteeg EJ, et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. Brain 2010;133(pt 6):1810–1822.
4. Rajput AH, Fenton M, Birdi S, Macaulay R. Is levodopa toxic to human substantia nigra? Mov Disord 1997;12:634–638.
5. Ormazabal A, Garcia-Cazorla A, Fernandez Y, Fernandez-Alvarez E, Campistol J, Artuch R. HPLC with electrochemical and fluorescence detection procedures for the diagnosis of inborn errors of biogenic amines and pterins. J Neurosci Methods 2005;142:153–158.
6. Pons R, Serrano M, Ormazabal A, et al. Tyrosine hydroxylase deficiency in three Greek patients with a common ancestral mutation. Mov Disord 2010;25:1086–1090.
7. Russel D, Rosenbaum P, Gowland C, et al. Gross Motor Function Measure Manual. 2nd ed. Hamilton, Ontario, Canada: McMaster University; 1993.
8. Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. Mov Disord 2007;22:1379–1389.
9. Cenci MA. L-dopa-induced dyskinesia: cellular mechanisms and approaches to treatment. Parkinsonism Relat Disord 2007;13(suppl 3):S263–S267.
10. Lee WT, Weng WC, Peng SF, Tzen KY. Neuroimaging findings in children with paediatric neurotransmitter diseases. J Inherit Metab Dis 2009;32:361–370.
11. Segawa M, Nomura Y, Nishiyama N. Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). Ann Neurol 2003;54(suppl 6):S32–S45.
12. Zhou QY, Palmiter RD. Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. Cell 1995;83:1197–1209.
13. Lin JP. The cerebral palsies: a physiological approach. J Neurol Neurosurg Psychiatry 2003;74(suppl 1):i23–i29.
14. Blanchet PJ, Konitsiotis S, Chase TN. Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. Mov Disord 1998;13:798–802.
15. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006;5:677–687.