

Autosomal Dominant Guanosine Triphosphate Cyclohydrolase I Deficiency (Segawa Disease)

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Autosomal dominant guanosine triphosphate cyclohydrolase I (GCH-I) deficiency (Segawa disease) is a dopa-responsive dystonia caused by mutation of the *GCH-I* gene located on 14q22.1-q22.2. Neurohistochemical examination revealed a decrease of the tyrosine hydroxylase protein as well as its activity in the striatum and decrease of dopamine content, particularly in its ventral portion rich in D1 receptors (striatal direct pathways). Neuroimaging, clinical neurophysiological, and biochemical studies showed preservation of the structure and function of the terminal of the nigrostriatal DA neuron. Clinical neurophysiological studies showed no progressive decrement of DA activities. As the enzymatic activity of pteridine metabolism is highest in the early developmental course, it may modulate dopamine receptors maturing early in the developmental course. Its product, tetrahydrobiopterin, has higher affinity to tyrosine hydroxylase among hydroxylases. Thus, partial deficiency of tetrahydrobiopterin caused by heterozygous mutation of the *GCH-I* gene decreases dopamine activity rather selectively. This affects the DA receptors that mature early and demonstrates characteristic symptoms age-dependently along with the developmental decrement of the tyrosine hydroxylase activities at the terminals and the maturational processes of the projecting neurons of the basal ganglia. A difference in the ratio of mutant/wild-type GCH-I mRNA that depends on the locus of mutation may explain intrafamilial and interfamilial variation of phenotype.

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Autosomal dominant guanosine triphosphate cyclohydrolase I (GCH-I) deficiency (Segawa disease) is a dominantly inherited dystonia that responds markedly to L-dopa and is caused by heterozygous mutation of *GCH-I* gene located on 14q22-q22.2. This disease was first described in 1971 as hereditary progressive basal ganglia disease with marked diurnal fluctuation.¹ This description was based on clinical evaluation of two children, cousins, each of whom had dystonic hypertonus that alleviated after sleep and responded markedly to L-dopa.¹ However, observations of an adult patient with a clinical course of 43 years revealed the characteristic age-related clinical course and clarified this disease as a dystonia different from Parkinson's disease. In 1976, we reported this disease as hereditary progressive dystonia with marked diurnal fluctuation.² Later, it was called dopa-responsive dystonia by Nygaard and colleagues,³ and its criteria were defined by Calne.⁴ With correlation of the age-related clinical course to the age variation of the activities of tyrosine hydroxylase (TH) in the caudate nucleus⁵ and marked sustained response to L-dopa, deficiency of TH at the terminal of the nigrostriatal dopamine (DA) neuron was suggested as the cause of this disease.^{6,7} This specula-

tion was confirmed later by a neurohistochemical study,⁸ and it was revealed to be due to the partial deficiency of tetrahydrobiopterin (BH4) caused by abnormalities of the *GCH-I* gene.⁹ Although the presence of intrafamilial and interfamilial variation of symptoms had been shown,¹⁰ the discovery of the causative gene further clarified heterogeneity of symptoms^{11,12} and also raised the question as to how a single gene mutation can cause this specific disorder age dependently.^{13,14} In this article, we demarcate characteristics of this disease by reviewing articles, including our recent investigations of our own patients, and we discuss the possible pathophysiology of this disorder.

Clinical Characteristics

The clinical characteristics of the classic autosomal dominant GCH-I deficiency are shown in Table 1, and the symptoms clarified after the discovery of the causative gene are shown in Table 2.

The clinical symptoms are characterized by their age dependency. It is shown in the natural course of the classic type. That is, it starts with postural dystonia of one extremity in childhood around 6 years, mostly as pes equinovarus, which expands to all limbs in the first

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Table 1. Main Characteristics of "Classic" Autosomal Dominant GTP Cyclohydrolase I Deficiency

Early occurrence in childhood/age-related clinical course
Diurnal fluctuation
Postural dystonia throughout the course
Postural tremor appears later
No parkinsonian resting tremor
Preservation of interlimb coordination
No mental or psychological abnormalities
No autonomic nervous symptoms
Marked sustained response to L-dopa without any side effects

Somatic symptom: deceleration of body length.

10 to 15 years with aggravation of dystonic hypertonus. Around the age of 10 years, the postural tremor appears in one upper extremity. The progression of dystonia subsides with age and becomes almost stationary in the fourth decade. Postural tremor continues to spread to other limbs; around the fourth decade, it appears on all extremities, including the neck muscles. Diurnal fluctuation decreases its grade along with the subsidence of the progression of dystonia and becomes unapparent clinically in the third decade. Asymmetry of symptoms is observed throughout the course of illness. Besides the neurological symptoms, deceleration of the body length appears in childhood with the onset of motor symptoms. Clumsiness of diadochokinesis or of pronation/supination movement of an upper extremity and failure in tilting response are observed from childhood, with side difference. Exaggeration of tendon reflexes is also observed in child patients. It associates with ankle clonus but without Babinski sign. Pulsions are observed mostly in the advanced stage, but it is due to rigid-akinetic type and not due to freezing. Because locomotion is preserved normally throughout the course of the illness, child patients can crawl with normal interlimb coordination, even though their gait lacks the upper limb coordination. Initiation of the movement is also preserved.

It is noteworthy that these clinical courses are dependent on age and not on the progression of the disease processes or dystonia.¹⁵ That is, patients with onset in the second decade tend to start with dystonia of the

Table 2. Phenotypical Variation Clarified after Detection of the Causative Gene

Focal dystonia: writer's cramp, guitarist's finger
Paroxysmal dystonia
Spontaneous reduction and exacerbation of dystonia
Dystonic spasm with or without pain
Action dystonia
Oculogyric crisis
Muscle hypotonia with delay in development in crawling ^a
Delay in development of language ^a

^a*Observed in patients with compound heterozygote

upper limbs with or without postural tremor. Those with onset in adulthood start with hand tremor without dystonia and diurnal fluctuation. Although there is mild dystonic hypertonus, it shows no apparent progression. Exaggeration of tendon reflexes is a characteristic feature of child patients, and short stature is not observed in patients with onset after late childhood. However, asymmetry of symptoms and female predominance are commonly observed without any relation to the age of onset.

Table 3 shows the symptoms observed in 28 gene-proved patients from 15 families. With the exception of one patient that had an age at onset at 58 years, all the patients had ages at onset in childhood, with an average of about 7 years. The child patients had ages at onset ranging from 16 months to 13 years and showed postural dystonia. The initial symptom started on the lower extremities in all but three of the patients, two of whom had onset in late childhood, and one of whom had onset in adult age. Diurnal fluctuation was not observed in the one patient with onset in adulthood. Short stature was not observed in these late-onset patients. On the other hand, postural tremor did not appear in 14 patients administered L-dopa before 10 years. The number of patients who had the symptoms shown in Table 2 was small. Among these symptoms were paroxysmal dystonia, dystonic cramp, and oculogyric crisis, which were observed in patients with action dystonia. We have reported two patients with action dystonia as having a different disease with a pathophysiology distinct from hereditary progressive dystonia or autosomal dominant GCH-I. Although these patients were different (a fact we established with

Table 3. Clinical Symptoms Observed in 28 Gene-Proved Patients from 15 Families

Age at onset	6.9 ± 2.6 years ^a (except one male with onset at 54 years)
Gender difference	F : M = 25 : 3
Initial symptoms	
Postural dystonia of one leg	25/28
Postural dystonia of one arm	1/28
Hand tremor or tremulous movement	2/28
Diurnal fluctuation	27/28 ^b
Asymmetry of symptoms	28/28
Postural dystonia of lower extremity predominance	27/28
Hand tremor, postural	14/28
Action dystonia	4/28
Torticollis	2/28
Dystonic spasm	2/28
Oculogyric crisis	1/28
Depressive state	1/28
Migrain headache	1/28

^aExcept one male with onset at 54 years.

^bExcept one patient with adult onset.

polysomnographic scans), they had a marked response to L-dopa.¹⁶ These lines of evidence suggest that pathophysiology for action dystonia cause heterogeneity of symptoms in autosomal dominant GCH-I deficiency.

Depression and migraine as well as autism are symptoms related to serotonin deficiency. Symptoms observed in compound heterozygote also might be caused by depletion of serotonin due to a marked decrease of BH4 (see below). Thus, for the heterogeneity of symptoms there are at least three factors. One is dependent on age at onset, the second on the pathophysiological differences, and the third on differences in the grade of decrement of BH4.

Investigations

Clinical Neurophysiological Studies

SURFACE ELECTROMYOGRAPHY. Surface electromyographs of adult patients with a clinical course of 30 years¹⁵ showed simultaneous contraction of the agonistic and antagonistic muscles and overflow of muscle contraction to the unrelated muscles by certain voluntary movements, particularly by a skillful movement. The stretch reflex induced tonic muscle contraction; however, in contrast to Parkinson's disease, it disappeared with repeating the examination. The Westphal phenomenon was often observed. The tremor was postural with a frequency of 6 to 8Hz, and occasionally it was 8 to 10Hz. However, it was 4 to 6Hz in a 59-year-old male patient with onset at 58 years (Segawa unpublished data). This tremor disappeared with the stretching of the muscle.

Surface electromyographs also revealed a difference in the side predominance of the hypertonus between the sternocleidomastoideus and the muscles of the extremities. However, in recent studies in the adult patients, we detected that the dominant side of tremor of the sternocleidomastoideus was ipsilateral to side of the extremities more affected, and that the side of torticollis observed in a 34-year-old female was also the same as the dominantly involved side of extremity (Segawa unpublished data). In the latter, dystonia occurred at 13 years and the torticollis appeared at 16 years. This suggests that pathophysiology for the postural dystonia differs from that for postural tremor or segmental dystonia in autosomal dominant GCH-I deficiency.

These findings from surface electromyography show that the hypertonus of autosomal dominant GCH-I deficiency is dystonia different from that observed in Parkinson's disease. These findings also revealed the heterogeneity of pathophysiology of this disorder.

POLYSOMNOGRAPHY. Polysomnographic scans revealed selective involvement of the phasic components of sleep, that is, twitch movements, gross movements, and rapid eye movements (REMs), while showing pres-

ervation of the tonic components, that is, restriction of atonia in stage REM sleep structure, and relative ratio of sleep stages.² However, in one patient with action dystonia and oculogyric crisis, leakage of the atonia of stage REM into NREM sleep (atonic non-REM) was observed.¹⁷

The twitch movements in stage REM decreased their number to around 20% of normal values,² and with these values the twitch movements followed the decremental age variation and incremental nocturnal variation observed in normal individuals.^{18,19} Although the grade of nocturnal variation decreased with age, there was no progressive reduction of the values against normal levels with age and with progression of the disease.¹⁸

The gross movements showed abnormalities in the rate of occurrence against sleep stages.² However, the pattern differed between those with postural dystonia and those with action dystonia.^{16,17}

The horizontal REMs were more often directed towards the side of the body with the extremity that was less severely affected, or the side of the hemisphere with the more severely affected nigrostriatal DA neurons.¹⁸⁻²⁰ The same characteristics of side preference were observed in hemiparkinsonism, but the preference was reversed in hemidystonia caused by the contralateral striatal lesion.¹⁸⁻²⁰ The side preference of the affected muscles estimated by the decrease of twitch movements in stage REM differed between the sternocleidomastoideus and those of extremities.²¹ This pattern was observed in a patient with hemiparkinsonism; however, in patients with symptomatic torsion dystonia with a striatal lesion, the side of predominance was ipsilateral in sternocleidomastoideus and limb muscles.

Diurnal fluctuation or sleep effect was abolished by selective stage REM deprivation. It was not affected, however, by selective slow-wave sleep deprivation (sleep stages IV and V).²

All of these abnormalities improved after L-dopa.^{2,18-20} However, the abnormalities of the pattern of gross movements observed in patients with action dystonia were not normalized even though they were completely improved clinically.^{16,17} In one of the patients with oculogyric crisis, atonic NREM was also observed after L-dopa.¹⁷

Each parameter of sleep reflects the activities of the neurotransmitter(s) specific for each.²² Polysomnographies of autosomal dominant GCH-I deficiency revealed normal preservation of components modulated by the cholinergic, noradrenergic, and serotonergic neurons of the brainstem. However, leakage of atonia of stage REM into atonic NREM observed in a patient with action dystonia implies dysfunction of the serotonin neurons of the brainstem, as the serotonin neurons of the dorsal raphe nucleus prevent the occurrence of the atonia of sREM in atonic NREM.²² The results of

deprivation of sleep at selected stages suggest that the pathophysiology of this disease depends on the neuronal events or the neurons involving stage REM. Twitch movements in stage REM reflect the activities of the nigrostriatal DA neurons. Thus, age and nocturnal variations of twitch movements in stage REM following these variations of normal subjects demonstrate the pathophysiology of the age-related clinical course and the diurnal fluctuation, respectively, and also show that the nigrostriatal DA neuron preserved its function of age and circadian variation.^{18,19} The absence of a progressive decrement in values of twitch movements against normal ones implies that there is no progressive reduction of the DA activities of the nigrostriatal DA neuron in autosomal dominant GCH-I deficiency.

Characteristics observed in the side preference of horizontal REMs and difference in the side predominantly affected (between the sternocleidomastoideus and limb muscle) confirm that the main lesion is in the nigrostriatal DA neuron and that the projecting pathways and other adjacent neurons in the basal ganglia are not affected primarily.

VOLUNTARY SACCADES. Visually guided saccade and memory-guided saccade of autosomal dominant GCH-I deficiency were examined by Hikosaka's method.²³⁻²⁶ In contrast to Parkinson's disease, autosomal dominant GCH-I-deficiency showed abnormalities in visually guided saccade with prolongation of the latency, hypometria, and reduced peak velocity. Memory-guided saccade revealed abnormalities with a decrease in the frequency of the memory-guided saccade, an increase in the frequency of the saccade to the target cue or destructed saccade (DS), hypometria, prolonged latency, and reduced peak velocity. These abnormalities in memory-guided saccade were milder than Parkinson's disease, except that of DS. Among the patients with autosomal dominant GCH-I deficiency, these abnormalities were more marked in patients with action dystonia than those with postural dystonia.^{17,26}

Among saccade neurons in the caudate nucleus and the substantia nigra pars reticulata, one third of the neurons are specific for visually guided saccade, and another one third of the neurons are specific for memory-guided saccade.^{27,28} Parameters of visually guided saccade show no age variation in individuals from 6 to 70 years, while those of memory-guided saccade do show age variation.²⁷ In memory-guided saccade, these parameters attain their maturational levels around 15 years, and they reflect the aging process from around 50 years.^{25,29}

These results of visually guided saccade suggest that the pathophysiology of autosomal dominant GCH-I deficiency differs from that of Parkinson's disease. They also suggest involvement of the neuronal path-

ways of the basal ganglia, which mature early, at least before 5 years.

The abnormalities of DS were considered to be caused by upward regulation of D2 receptor, which may not involve disease processes essentially because the levels of abnormalities declined with age following the age-related declining process of normal children. Alternatively, this may be due to delay in developmental decrement of the D2 receptors, as the number of D2 receptor is high in younger patients and decreases with age, with these receptors attaining their mature levels in patients in their thirties.³⁰

Biochemical Examination

A decrease of homovanillic acid in cerebrospinal fluid was detected in early studies.³¹ Reduction of 3-methoxy-4-hydroxyphenylglycol and not of 5-hydroxyindole acetic acid was also observed early.³² However, a decrease of pteridin metabolites, neopterin as well as biopterin, in cerebrospinal fluid (less than 20% of normal values detected by Fujita and Shintaku³³ and by Furukawa and colleagues³⁴) is the most characteristic finding for autosomal dominant GCH-I deficiency. Hyland and colleagues³⁵ showed abnormalities in the pheynylalanine-loading test.

Ichinose and colleagues⁹ demonstrated a marked decrease (to below 20%) of the activities of GCH-I in peripheral mononuclear blood cells. Bezin and colleagues³⁶ showed similar results by estimating enzyme levels in cultured lymphocytes.

Takahashi et al.³⁷ examined the neopterin and biopterin levels in the cerebrospinal fluid of asymptomatic carriers and revealed a mild decrement (30 to 50%). Ichinose and colleagues⁹ also showed a moderate decrement (30 to 40%) of the activities in asymptomatic carriers.

These biochemical studies clearly revealed a decrease of DA and serotonin in autosomal dominant GCH-I deficiency and a decrease of GCH-I as the cause of this disease. These studies also showed the extent of the decrement of the enzyme may differ among individuals with the mutant gene.

Neuroimaging Studies

Positron emission tomography with [¹⁸F]L-dopa showed normal³⁸ or below normal³⁹ incorporation of dopa at the terminal of the nigrostriatal DA neuron. [¹¹C]Raclopride positron emission tomography revealed normal incorporation,⁴⁰ but another study with [¹¹C]N-spiperone positron emission tomography showed mild upward regulation of the D2 receptors.⁴¹ Kishore and colleagues⁴² showed mild elevation of raclopride incorporation, but they found no alteration of the results in another study performed after a 7-month treatment with L-dopa. They concluded that the increase of D2 receptor binding in this disease is a

homeostatic response to the DA deficiency state and not a factor determining the clinical state.⁴² Jeon and colleagues⁴³ showed normal DA transporter density by [¹²³I]β-CIT single positron emission tomography.

We performed [¹⁸F]L-dopa and [¹¹C] spiperon positron emission tomography on three L-dopa-naïve adults, two 38-year-old females with clinical histories of 30 years, and one 59-year-old male patient with onset at 58 years. Our scans showed no abnormalities (Momose, unpublished data).

These neuroimaging results confirm the normal preservation of the structure of the nigrostriatal DA neuron. In addition, they imply that a decreased TH level is the main pathology of autosomal dominant GCH-I deficiency³⁸ and that the DA-D2 receptors are not involved or have no essential pathophysiological role.⁴² Furthermore, it is revealed that the function of the nigrostriatal DA neuron does not change with L-dopa treatment, longevity of the clinical course, or age at onset.

Neuropathology and Neurohistochemistry

The first neuropathological⁴⁴ and neurohistochemical⁸ examinations were performed on the autopsied brain of an 18-year-old female with L-dopa-responsive dystonia. It was later revealed, after analysis of DNA from brain tissue, that the patient had autosomal dominant GCH-I deficiency.⁴⁵ Neuropathology revealed no abnormalities (except decrease of melanin pigments) in the substantia nigra or in the basal ganglia. Neurohistochemistry revealed a decrease of the DA content both in the striatum and the substantia nigra, though it was milder than the decreases observed in idiopathic Parkinson's disease. Regionally, the DA content was decreased more prominently in the putamen than in the caudate nucleus. In the subregional rostro-caudal gradient, a prominent decrease of DA content was revealed in the rostral region of the caudate and the caudal region of the putamen, as observed in idiopathic Parkinson's disease. However, in the subregional dorso-ventral gradient, DA content was markedly decreased in the ventral area, in contrast to the dorsal predominance of idiopathic Parkinson's disease. TH protein content as well as its activities were decreased in the striatum, but they were normal in the substantia nigra.

Recently, Furukawa and colleagues⁴⁶ showed similar results on two autopsied brains; that is, in the striatum, TH protein concentration as well as TH activities were decreased, especially in the putamen (by as much as 97%). However, these investigators did not comment on the content of DA in the dorso-ventral subregional gradient. Furukawa and colleagues⁴⁶ also revealed marked reductions of total biopterin (by 84%) and neopterin (by 62%) concentrations in the putamen of these patients. Most biopterin exists as BH₄, and neopterin is generally considered to reflect the activity of

GCH. Furthermore, these investigators showed normal preservation of striatal levels of L-dopa decarboxylase protein, dopamine transporter, and vesicular monoamine transporter.

Furukawa and colleagues⁴⁷ examined an autopsied brain of an asymptomatic GCH-I mutation carrier and found only modest reductions of TH protein (by 52%) and DA (by as much as 44%) despite a marked reduction of biopterin (by 82%) in the putamen.

The particular regional and the rostro-caudal subregional reductions of DA content, which resemble those in idiopathic Parkinson's disease, are considered responses of normal striatum to the depletion of DA secretion from the nigrostriatal DA neurons.⁴⁸ Moreover, they suggest that in these diseases, the striatum is free of a primary lesion. Studies on the compartmental substructure of the human striatum revealed that within the rostral caudate in particular, the medial/ventral portions of the nucleus striosomes/patches or D1 direct pathways were more numerous, whereas in the dorsal/lateral portions the matrix compartment was more homogenous.^{49,50} Thus, Hornykiewicz⁸ suggested that the DA loss in hereditary progressive dystonia (L-dopa-responsive dystonia) or autosomal dominant GCH-I deficiency is more prominent in the striosomes/patches compartment, and that in Parkinson's disease the DA loss is more prominent in the matrix or D2 indirect pathways. These histochemical findings, which show predominant reduction of DA in the striatum, suggest that striatal DA nerve terminals are preserved in autosomal dominant GCH-I deficiency.⁴⁶ The striatal DA reduction in autosomal dominant GCH-I deficiency is caused not only by decreased TH activity resulting from low cofactor concentration, but also by actual loss of TH protein in the striatum.⁴⁶ The extent of striatal TH protein loss may play an important role in determining the symptomatic state of autosomal dominant GCH-I deficiency.⁴⁷

Molecular Biology

According to Furukawa⁵¹ more than 85 independent mutations have been identified in the coding region (including the splicing junctions) of GCH-I. The locus of mutation differs among families but is identical in one family. However, Furukawa and Kish¹³ also showed that no mutation in either the coding region or the splice site of GCH-I was demonstrated in approximately 40% of L-dopa-responsive dystonia families. These investigators used conventional genomic DNA sequencing of the six exons of the gene. In our own cases, we could not detect any abnormalities of the GCH-I gene in 4 of 19 families (21%). In these four families, two had dominant inheritance, and two lacked familial occurrence.

For the families that had a mutation-negative coding region, L-dopa-responsive dystonia, and biochemical

dysfunction related to GCH-I, Furukawa⁵¹ proposed the following possible explanations: 1) a mutation in noncoding regulatory regions of GCH-I; 2) a large genomic deletion of one or more exons of GCH-I; 3) an intragenic duplication or inversion of GCH-I; and 4) mutations in as yet undefined regulatory genes that result in products capable of interacting with GCH-I and modifying enzyme function.

Actually, we detected abnormalities at intron 3 in two families and at intron 4 in one family. There were reports detecting point mutations in the 5'-untranslated region of GCH-I.^{11,12} Furukawa and colleagues⁵² found a large genomic deletion in GCH-I that was undetectable by the usual genomic DNA sequence analysis. Inagaki and colleagues⁵³ reported that GCH-I mRNA amounts were decreased to about 40% of the normal level in one of our families. They also showed that GCH-I mRNA was transcribed from only one allele by utilizing the length polymorphism that exists at exon 6. This suggests that events at the transcriptional level of the GCH-I gene may help explain the enzyme activity in autosomal dominant GCH-I deficiency.⁵⁴ Recently, we found a mutation at the exon 3-intron 3 splice junction site in this family, a mutation that for no known reason remains unidentified. Since the newly identified mutation at the exon 3-intron 3 splice junction site would give exon-3 skipping, the reduction of GCH-I mRNA, which was examined by two sets of primers (exon 1 to 3 and exon 3 to 6), was reasonably explained. Moreover, because exon-3 skipping would produce early truncation of GCH-I mRNA, the length polymorphism analysis of exon-6 mRNA might apparently produce single-allele expression.

Differential Diagnosis

Autosomal dominant GCH-I deficiency is often misdiagnosed as hereditary spastic paraplegia or cerebral palsy. A few patients were first misdiagnosed as having hysteria or Duchenne muscular dystrophy. Although clinical features have characteristics similar to those of autosomal dominant GCH-I deficiency, hereditary spastic paraplegia and cerebral palsy can be differentiated clinically with careful history taking and neurological examinations.

The most important disorders that should be differentiated are L-dopa-responsive disorders that occur in childhood. They are disorders included in the pediatric neurotransmitter disorders and juvenile parkinsonism, which occasionally has onset in childhood. Alternatively, autosomal dominant GCH-I deficiency that occurs in adulthood and senior ages should be differentiated from idiopathic Parkinson's disease.

Among pediatric neurotransmitter disorders, those with abnormalities in pteridine metabolism include recessive GCH-I deficiency, recessive tetrahydropterin

synthase deficiency, and recessive dehydropterin reductase deficiency. Although all of these abnormalities show dystonia, they have marked postural hypotonia, abnormalities of locomotion, and psychomotor disturbances that are due to hypofunctioning of the serotonin neurons caused by marked reduction of BH₄.⁵⁵ The effect of L-dopa is not marked, and it is necessary to add BH₄ or 5-hydroxytryptophan.⁵⁵

Recessive TH deficiency caused by mutation of *TH* gene on 11p15.5, first reported as a recessive variant of Segawa syndrome,⁵⁶ showed dystonia responsive to L-dopa. They showed marked heterogeneity of symptoms, including psychomotor disturbances,⁵⁷ but some showed features of spastic paraplegia, which responded to L-dopa.⁵⁸ Furukawa and colleagues⁵⁸ recommends analysis of *TH* gene for sporadic patients with L-dopa-responsive dystonia or L-dopa-responsive dystonia patients without family histories in which mutation of GCH-I gene could not be detected.

Juvenile parkinsonism may occur in childhood with dystonia as the main symptom, and autosomal recessive juvenile parkinsonism with abnormalities in the *parkin* gene shows diurnal fluctuation.^{59,60} In these patients, parkinsonism appears in the later half of the second decade. For these patients, L-dopa shows marked effects, but soon the doses must be increased, and dyskinesia appears. The L-dopa-induced dyskinesia developed in childhood or in the second decade in juvenile parkinsonism is intractable and requires stereotactic operation. However, the effect of operation was sometimes not favorable.⁶¹ Thus, it is necessary to differentiate juvenile parkinsonism carefully. If exclusive reliance on L-dopa in the early period of the treatment would necessitate higher doses, treatment should resort to dopa agonists, which would allow the doses of L-dopa to be reduced.

Thus, for diagnosis of autosomal dominant GCH-I deficiency, analysis of the causative gene is necessary. However, as the gene abnormalities are not detected in all patients with autosomal dominant GCH-I deficiency, the most reliable means of diagnosis is the estimation of neopterin and biopterin in the cerebrospinal fluid, or the estimation of GCH-I activity in the mononuclear cells of the peripheral blood.

Treatment and Prognosis

L-Dopa shows marked and sustained effects without any relation to the longevity of the clinical courses.^{2,62,63} L-Dopa improves all neurological symptoms and reduces stagnation of body length if it is administered in childhood. The maximum or optimal dose is around 20mg/kg per day (plain L-dopa without decarboxylase inhibitor).⁶¹ An aggravation of symptoms after the initial dose was observed in patients with action dystonia^{6,17} and compound heterozygote.⁶⁴ In a few patients, choreic movement developed if the treatment

was started with a relatively high dose of L-dopa or if doses increased rapidly.⁶² However, these unfavorable symptoms soon disappeared after the withdrawal of L-dopa; moreover, they did not reappear if L-dopa was resumed at a lower dosage and if doses were increased in smaller amounts.

Dissatisfaction with plain L-dopa has been expressed on behalf of patients (or by the patients themselves) who were around 10 to 15 years of age, and for whom L-dopa therapy had started in childhood, before 10 years of age.⁶² Complaints about the ineffectiveness of plain L-dopa depended on the extent of decarboxylation of the L-dopa in the intestines.⁶² Decarboxylation was marked in childhood, but in some patients the activity decreased when they reached the age of 12 to 13 years; in other patients, the activities continued with high levels after these ages. In the latter group, the effects of plain L-dopa were reduced in these ages. In these patients, administration of L-dopa with carbidopa improved the effect.

L-Dopa-loading tests performed repeatedly during the course of treatment showed no alteration of the absorption course of L-dopa.⁶⁵ That is, the peak was at 2 hours after oral L-dopa without any relation to the longevity of the treatment. This suggests that the functions of the terminal of the nigrostriatal DA neuron and the DA receptors are normally preserved or are not affected by prolonged administration of L-dopa.

In our experience, 7 of 28 gene-proved patients have been under L-dopa for more than 30 years. Of these seven patients, five began receiving treatment in childhood (from around 3 to 11 years), and two began receiving treatment in adulthood (one was 41, and the other was 51 years of age). Apart from these seven patients who have been under treatment for over 30 years, there is a group of five patients who have been under L-dopa for more than 20 years, four from the childhood (around 6 to 12 years), and one from an age of 34 years. In all the patients, L-dopa continues to show benefits without imposing any side effects.

Anticholinergics also show marked and sustained effects both on postural dystonia and postural tremor, although the effects were not complete.^{66,67} In a few patients,⁶⁸ particularly those with compound heterozygotes,⁶⁴ administration of BH4 or 5-hydroxytryptophan in addition to L-dopa was necessary for complete recovery.

Unilateral stereotactic pallidotomy and ventrolateral thalamotomy were performed before the era of L-dopa on a 73-year-old female who had an age of onset of 6 years.⁶⁹ The pallidotomy performed at 30 years improved postural dystonia and dystonic spasm, and the ventrolateral thalamotomy performed later at 37 years on the same side was effective on postural tremor and repetitive grouping discharges that had been detected with electromyography. However, the effect of pal-

lidotomy on postural dystonia was incomplete, and the thalamotomy showed no further effects on the dystonia that remained after the pallidotomy. Complete recovery of the postural dystonia was obtained after administration of L-dopa from 34 years, but the effect was not complete on the side of the operation.

In all, the effects of L-dopa were sustained without any side effects. Thus, the prognosis of autosomal dominant GCH-I deficiency is favorable with L-dopa, although in some patients the depletion of serotonin must be adjusted.

Pathophysiology

The Nigrostriatal DA neuron(s) and the Pathway(s) in the Basal Ganglia Involved in Autosomal Dominant GCH-I Deficiency

McGeer and McGeer⁵ revealed marked age variation in the activities of TH at the terminals of the nigrostriatal DA neuron. The activities are highest in early childhood and show exponential decreases with age in the first three decades. The decreases are marked in the first decade, but they become moderate in the second decade and slight in the third decade. Lastly, from the fourth decade, the activities become stationary, lacking any age variation. In the substantia nigra, TH activities show no apparent age variation.⁵

The age-related decreases of the TH in the caudate nucleus are present; moreover, they are well correlated with the clinical course, with activity levels reduced to around 20% of normal values.^{6,7} The marked and sustained response to L-dopa without any side effects suggests a functional disorder of the nigrostriatal DA neuron without any morphological changes. This possibility prompted us to hypothesize that the cause of this disease is the decrease of TH activity in the striatum or at the terminal of the nigrostriatal DA neuron.^{6,7,70} Age-related changes of twitch movements in stage REM supported this hypothesis. With this lesion, diurnal fluctuation of symptoms is also explained because the activities of TH show circadian oscillation at the terminal,⁵ and there are no phase-related changes of unit activity of the DA neurons in the substantia nigra.⁷¹

Neuroimaging, neuropathological, and neurohistochemical studies confirmed normal preservation of the nigrostriatal DA neuron. Polysomnography showed that the terminals of the nigrostriatal DA neuron preserve their function of age and nocturnal variation normally.

Neurohistochemical examinations suggest predominant involvement of the nigrostriatal DA neuron, which connects to the D1 receptor on the striatal direct pathway. Nunes Junior and colleagues⁷² showed that paradoxical sleep deprivation increases D2 but not D1 receptor binding in rat brain. This suggests that

selective REM sleep deprivation decreases DA content in the brain, which may affect the processes related to D1 but not D2 receptors because of their upward regulation. The results of the selective deprivation study on autosomal dominant GCH-I deficiency suggest involvement of the nigrostriatal DA neuron related to the D1 receptors.

However, the pattern of gross movements observed in polysomnographic scans of patients with action dystonia suggests DA-receptor supersensitivity. Marked involvement of memory-guided saccade in these patients also suggests involvement of the striatal indirect pathway. Furthermore, the presence of atonic NREM also implies involvement of serotonin neurons.

The difference of the side preference of the dystonic hypertonus between the sternocleidomastoideus and the muscles of the extremities observed in clinical and polysomnographic studies suggests that the lesion for the postural dystonia ranges from the afferent to the striatum, that it is, in fact, the nigrostriatal DA neuron. However, the identical side preference of postural tremor implies that the lesion for the tremor is in the basal ganglia. We speculate that the D1 receptor is involved, on the subthalamic nucleus, as suggested by Walter's group.^{73,74} Hypofunctioning of the DA neurons projecting to this receptor could cause hypofunctioning of the subthalamic nucleus, which might induce rhythmic oscillation by disturbing the neuronal circuit, including the external and internal globus pallidus. The D1 receptor on the subthalamic nucleus may also involve in the pathophysiology of action dystonia.

A small lesion in the area of the ventralis oralis posterior (Vop) nucleus and the ventralis intermedius (Vim) nucleus of the thalamus sometimes relieved dystonia.⁷⁵ The proportion of sensory cells was greater in the Vim nucleus than the Vop nucleus in patients with dystonia, and a significantly greater proportion of cells in the Vop nucleus than in the Vim nucleus are demonstrated by dystonia frequency activity.⁷⁶ The Vop nucleus has a direct connection to arm motor cortex and to the supplementary motor area,⁷⁷ both of which project to the spinal cord.⁷⁸ The supplementary motor area influences movement-related activity in the motor cortex.⁷⁹ Thus, Zirh and colleagues⁷⁶ suggested that the Vop nucleus influences electromyographic activity in dystonia by transmission of dystonia-related activity to the spinal cord through the supplementary motor area or indirectly through the motor cortex.

Autosomal dominant early-onset torsion dystonia with ages at onset similar to autosomal dominant GCH-I deficiency has same phenotypes of postural and action dystonia depending on family,⁸⁰ and clinical characteristics of these two phenotypes are similar to the phenotypes of autosomal dominant GCH-I deficiency, except for the failure to respond to L-dopa.¹⁷

The results of the stereotactic operation on early-onset torsion dystonia suggest involvement of the output projection to the Vop nucleus of the thalamus for action dystonia. This target for action dystonia was not effective for postural dystonia of lower limbs associated in these patients.⁸⁰ Thus, action dystonia of autosomal dominant GCH-I deficiency may appear through the same output pathway to the Vop nucleus as that for the dystonia in early-onset torsion dystonia.

For postural dystonia, the other output pathway of the basal ganglia should be involved. We suggest the descending pathway to the reticulospinal tract^{81,82} as the responsible output pathway for postural dystonia. Through this tract, the decrease of TH at the terminal may induce exaggeration of the tendon reflex with ankle clonus, but without Babinski sign, as well as postural dystonia.

The results of the stereotactic operation performed in one case revealed that the basal ganglia output to the ventrolateral nucleus of the thalamus is involved in postural tremor but not in the postural dystonia of this disease. Involvement of voluntary saccade suggests involvement of the basal ganglia output projecting to the superior colliculus. On the other hand, preservation of locomotion suggests that the output projection to the neurons in the pedunclopontine nucleus involved in locomotion is left unaffected.

The pathophysiologies of the symptoms, which may now be observed in light of the discovery of the causative gene, are considered as follows. With reference to the results of stereotactic operation, dystonic muscle spasm is considered to develop through the reticulospinal pathways via the descending output of the basal ganglia, the same pathway as for postural dystonia.

The oculogyric crisis observed in patients with compound heterozygotes may be caused by the state of hypofunctioning of the indirect pathway due to upward regulation of the D2 receptors, a regulation that is induced by a marked decrease of BH4 (Watanabe, personal communication). Oculogyric crisis is observed in a patient with action dystonia with heterozygotic mutation. This patient had atonic non-REM and relatively low GCH-I activities, and was suggested to have lower BH4 levels.¹⁷ In this patient, the oculogyric crisis showed a response to L-dopa similar to action retrocollis.¹⁷ Thus, the same output pathway as that for action dystonia might be involved in the oculogyric crisis.

Upper generation of the proband with action dystonia of early-onset torsion dystonia shows focal dystonia.⁸⁰ Changes in the somatosensory maps caused by dysfunction of the supplementary motor area may be related to the occurrence of dystonic movements through a sensory/motor mismatch.⁷⁵ Zirh and colleagues⁷⁶ suggested this process occurred particularly in task-specific dystonia. Thus, the output pathway of the basal ganglia to the Vop nucleus of the thalamus for

action dystonia might also be involved in focal dystonia of autosomal dominant GCH-I deficiency through dysfunction of the supplementary motor area. For segmental dystonia of autosomal dominant GCH-I deficiency, a pathophysiology similar to focal dystonia is suggested.

Asymmetry of symptoms is considered a characteristic feature of the primary disorder of the nigrostriatal DA neuron because this neuron primarily has asymmetry in function. Ichinose and colleagues⁹ showed a gender difference in the activity of GCH-I in peripheral mononuclear blood cells. However, it is not confirmed. Furukawa and colleagues⁸³ showed a gender difference with respect to the penetrance; that is, it was much higher in females (87%) than in males (38%). In our studies on 47 individuals from 15 gene-proved families, we acquired identical figures: 26/30 (87%) in females, and 6/17 (35%) in males. Thus, marked female predominance might depend on a genetically determined gender difference of the DA neuron.⁸⁴

For the L-dopa-responsive stagnation of body length, involvement of the tubuloinfundibular DA neuron is suspected (see below). Thus, the nigrostriatal DA neuron and the neuronal pathways for motor symptoms observed in autosomal dominant GCH-I deficiency with postural and action dystonia are suggested, as shown in Figures 1 and 2. In compound heterozygotes, the pathophysiology might be modified with an increase in upward regulation of the D2 receptors.

Roles of the Mutated Gene for Pathophysiology of autosomal dominant GCH-I Deficiency

It is necessary to explain why a heterozygous mutation causes 1) a decrease in GCH-I activities to the levels of clinical manifestation, 2) interfamilial and intrafamilial variation of clinical symptoms, 3) a decrease in TH levels predominantly among hydroxylases, 4) a decrease in the concentration of TH protein in the striatum as well as its activities, 5) preferential involvement of the nigrostriatal DA neuron projecting to the D1-direct pathway, and 6) the role of this preferential involvement in the development of characteristic clinical symptoms through the particular pathways of the basal ganglia shown above.

There are no conclusive answers to these questions, but several ideas have been proposed. For the first question, a classic dominant negative effect is being considered^{85,86}; for the answer, however, a destabilizing effect of the mutant subunit is being considered.⁸⁷ Furthermore, the ratio of mutant/wild-type GCH-I mRNA in lymphocytes was higher in an affected individual than an affected heterozygote in Japanese families,^{88,89} and it also varies depending on the locus of the mutation.^{84,88,89} These are caused by inactivation of normal enzyme by mutant enzyme^{88,89} and may

cause intrafamilial variation as well as the rate of penetrance and interfamilial variation, respectively. The locus of mutation differs among families; thus, the phenotypical variation is considered to depend on the locus of mutation.

With respect to the third question, the difference in distribution of GCH-I mRNA in dopaminergic and serotonergic neurons⁹⁰ and the destabilization of the molecule of TH or impairment of axonal transport⁴⁷ are considered. We considered the difference of K_m value for TH and phenylalanine hydroxylase.⁹¹ That is, in autosomal dominant GCH-I deficiency with heterozygotic mutant gene, the BH4 level is partially decreased, such that TH with high affinity to BH4 may be selectively affected. Actually, muscle hypotonia and the failure in locomotion observed in patients with compound heterozygotes⁶⁴ are the symptoms caused by deficiency of serotonin, which is caused by a marked decrease of BH4 due to the presence of paired mutant genes.

The striatal DA reduction in this disorder is caused not only by decreased TH activity resulting from reduced cofactor concentration, but also by actual loss of TH protein. Thus, the two abnormal gene products identified so far in autosomal dominant GCH-I deficiency are related to TH molecules (Furukawa, personal communication).

Striatal TH loss in the substantia nigra, where striatal TH molecules are synthesized, was normal in two autosomal dominant GCH-I deficiency patients, so Furukawa and colleagues⁴⁶ suggested that BH4 could control stability rather than expression of this enzyme protein. This speculation was confirmed in two subsequent reports. In one report, Leff and colleagues⁹² presented gene transfer data and suggested a role for stabilization of TH protein by co-expression of GCH-I in vivo. In the other report, Sumi-Ichinose and colleagues⁹³ showed loss of TH protein but not of TH mRNA in the brains of BH4-deficient mice, that is, 6-pyruoyltetrahydropetrin synthase gene-null mice.

To answer the fifth question, it is intriguing to consider the pathophysiology of the stagnation of the body length that appears in early childhood in autosomal dominant GCH-I deficiency. As it is an L-dopa-responsive stagnation, we consider the tubuloinfundibular DA neuron as a responsible neuron, which modulates hypothalamic function via the D4 receptor. The D4 receptor belongs to D2 family but matures earlier than D2 receptors.⁹⁴

It is shown that the pteridine metabolism has a critical period beginning early in infancy and extending to early childhood.⁹³ In addition, the D1-direct pathways mature earlier, and the D2-indirect pathways mature later.^{95,96} Thus, the DA neuron in which the DA synthesis is modulated by pteridine metabolism might regulate DA receptors that mature early in the develop-

Postural dystonia type

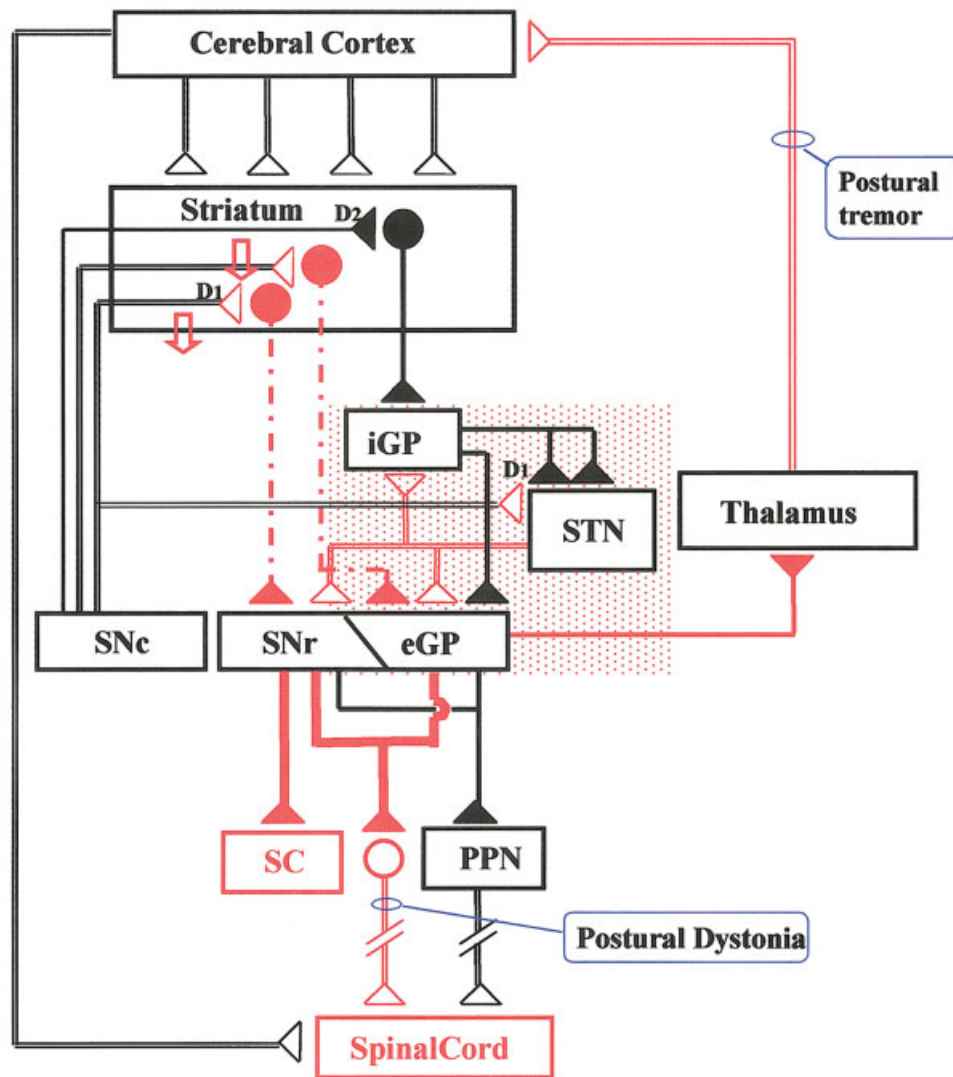


Fig 1. Postural dystonia type. Abbreviations: eGP = external segment of globus pallidus; iGP = internal segment of globus pallidus; STN = subthalamic nucleus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; SC = superior colliculus; PPN = pedunculopontine nucleus. Symbols: red lines = pathways involved in pathophysiology; black lines = pathways not involved in pathophysiology; solid line = inhibitory neuron; open line = excitatory neuron; closed triangle = inhibitory neuron; open triangle = excitatory neuron; shaded region = the area of the circuit for postural tremor.

mental course. All of the inherited disorders of pteridine metabolism develop dystonia.⁵⁵ All this evidence suggests that autosomal dominant GCH-I deficiency with decreased BH₄ levels early in the developmental course affects DA receptors that mature early.

A certain lesion in the basal ganglia or in the nigrostriatal DA neuron can lead to the development of particular symptoms, but only when the adjacent structures or the neurons or neuronal pathways downstream of the lesion are preserved in their normal state. In the developmental course, the symptoms can appear only

after these neurons (not only the lesioned neuron but also related neurons or neuronal pathways to the lesion site) mature to certain levels. These developmental variations of the nigrostriatal DA neurons and the basal ganglia could modulate the age at onset and clinical courses of the diseases with abnormalities in the nigrostriatal DA neuron or the basal ganglia that occur in these age periods.⁹⁶

Autosomal dominant GCH-I deficiency with non-progressive decrease of TH protein at the terminal of the nigrostriatal DA neuron affects DA receptors that

Action dystonia type

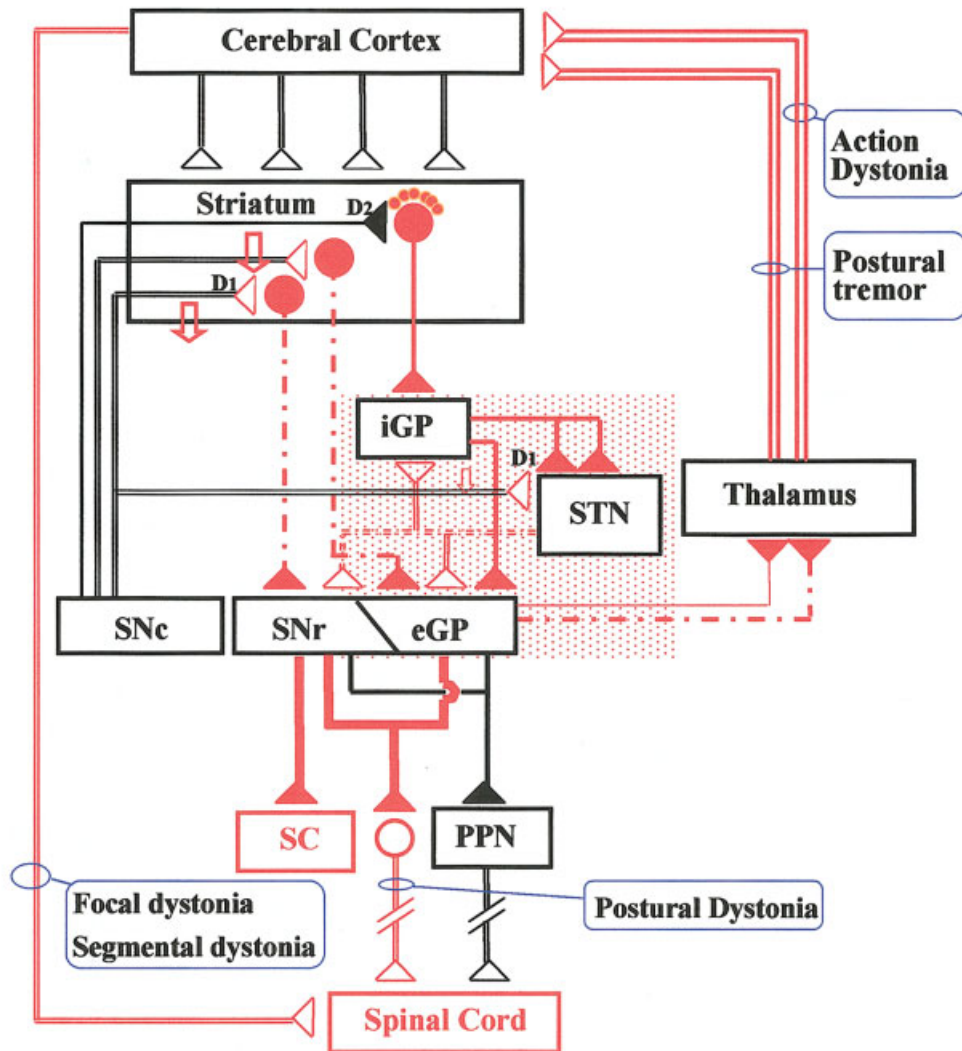


Fig 2. Action dystonia type. Abbreviations: eGP = external segment of globus pallidus; iGP = internal segment of globus pallidus; STN = subthalamic nucleus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; SC = superior colliculus; PPN = pedunculopontine nucleus. Symbols: red lines = pathways involved in pathophysiology; black lines = pathways not involved in pathophysiology; solid line = inhibitory neuron; open line = excitatory neuron; cluster of small, closed circles = upward regulation of the D2 receptors; closed triangle = inhibitory neuron; open triangle = excitatory neuron; shaded region = the area of the circuit for postural tremor.

mature early in the developmental course. In addition, this condition age-dependently manifests the specific symptoms from early childhood along with the maturational processes of the nigrostriatal DA neuron, related striatal projection neurons, and the output projection of the basal ganglia.¹⁵

In early developmental courses of the brain, the DA neurons as well as the serotonin and the noradrenergic neurons have roles for morphogenesis as well as for neurotransmission. During the fetal period, these neurons modulate the development of neuronal pathways

for specific functions. In the early postnatal period or during early infancy, they have roles for the development of neuronal networks for higher cortical functions such as cognition.⁹⁷ For the former processes, the neuronal activity of stage REM or active sleep has a role in activity-dependent neuronal development.⁹⁷ Among components of stage REM, twitch movements as well as REMs appear earliest in the developmental course, at around 20 weeks of gestation.⁹⁷ Among the sleep parameters in autosomal dominant GCH-I deficiency, the phasic components, particularly those of

stage REM, show abnormalities. Thus, hypofunction of GCH-I might cause dysfunction of the DA neuron that modulates the neuronal pathways early in the development, but might have no influence on the DA neuron that has developmental roles within the central nervous system for higher cortical functions.

Further study is necessary to confirm these speculations. In addition, it is necessary to clarify the pathophysiologies with which a heterozygous maturation of the GCH-I gene decreases TH protein in the striatum and affects particular nigrostriatal DA neurons and the neuronal pathways of the basal ganglia depending on the locus of the mutation.

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