The genetics of Segawa disease

Masaya Segawa

Segawa Neurological Clinic for Children, 2-8 Surugadai, Kanda, Chiyoda-ku, Tokyo 101-0062, Japan
■ Tel.: +81 3 3294 0371 ■ Fax: +81 3 3294 0290 ■ segawa@segawa-clinic.jp

Segawa disease is a dopa-responsive generalized dystonia, caused by abnormalities of the gene *GCH-1* located on chromosomes 14q22.1–q22.2. Clinically, there are two types, postural type and action type, depending on the family. Cases of action type show focal or segmental dystonia after adolescence. In families of action type, there are cases starting with focal or segmental dystonia in adulthood or parkinsonism in older age. Both types show symptoms of dopamine decrement due to the deficiency of tyrosine hydroxylase in the terminal of the nigrostriatal dopamine neuron, which is caused by *GCH-1* deficiency. With an onset in childhood, stagnation of body length develops. For these symptoms, L-dopa demonstrates dramatic effects. In early-onset cases, tryptophan hydroxylase is also affected and patients show symptoms of serotonin deficiency. More than 100 mutations of the *GCH-1* gene are detected; they are particular for each family. However, there is no particular mutation for postural and action type.

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Release date: 3 May 2013; Expiration date: 3 May 2014

Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the clinical characteristics and course of Segawa disease, based on a review
- Describe the genetics of Segawa disease, based on a review
- Describe the neurophysiology underlying Segawa disease, based on a review

Financial & competing interests disclosure

Editor: *Elisa Manzotti, Publisher, Future Science Group. Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.*

CME author: *Laurie Barclay, MD, is a freelance writer and reviewer, Medscape, LLC. Disclosure: Laurie Barclay, MD, has disclosed no relevant financial relationships.*

Author & credentials: *Masaya Segawa, MD, PhD, Segawa Neurological Clinic for Children, 2-8 Surugadai, Kanda, Chiyoda-ku, Tokyo 101-0062, Japan. Disclosure: Masaya Segawa has disclosed no relevant financial relationships.*

No writing assistance was utilized in the production of this manuscript.

Keywords

- action type ■ age dependency of symptoms
- diurnal fluctuation
- dopa-responsive dystonia
- gender difference
- hereditary progressive dystonia with marked diurnal fluctuation ■ postural type
- Segawa disease

In 1976, Segawa *et al.* reported a dystonia with onset in childhood, which responded to L-dopa as “hereditary progressive dystonia (HPD) with marked diurnal fluctuation” [1]. In 1988, Nygaard *et al.* proposed the nomenclature of dopa-responsive dystonia (DRD) for this disease [2]. Recently, the term DRD is used broadly for all dystonias that respond to L-dopa. Thus, in this article, the clinical characteristics, pathophysiology and genetics of Segawa disease are reviewed as a representative DRD.

Clinical characteristics of Segawa disease

In 1971, Segawa *et al.* reported two female cousins with dystonia, which aggravated toward evening but improved in the morning after sleep, and responded dramatically to L-dopa [3]. In 1976, with an increasing number of cases, particularly with experience of a 51-year-old female with non-treatment clinical course of 43 years after onset at 8 years (a grandmother of one case), Segawa confirmed this disease as dystonia, which does not convert to Parkinson’s disease in the elderly, and proposed the nomenclature of HPD [1].

This case started with postural dystonia of the right leg with muscle hypertonus when the patient was approximately 8 years of age, demonstrating diurnal fluctuation that was aggravated toward the evening and alleviated in the morning after sleep. Postural dystonia expanded to all limbs and the trunk by the midteenage years of the patient, with a postural tremor being recognized from approximately 10 years of age. However, the progression of dystonia and muscle hypertonus subsided in her late teenage years and the dystonic symptoms and hypertonus became stationary in her twenties. The tremor expanded to all limbs by the time the patient was in her twenties, but the progression subsided with age and became stationary in her early thirties. With subsiding progression of dystonia and hypertonus, diurnal fluctuation also subsided. There were no neuropsychological abnormalities. By examining this patient, the hypertonus was confirmed as rigidity. L-dopa was administered from when the patient was 51 years old and 100-mg carbidopa/L-dopa per day demonstrated dramatic effects, which continued without any side effects until the patient passed away from lung cancer at the age of 90 years. The clinical course of this case represents the clinical course of HPD. Furthermore, this clinical course is well explained by following age-dependent decrement of tyrosine hydroxylase (TH) in the terminal of the nigrostriatal (NS) dopamine (DA) neuron

shown by McGeer and McGeer (FIGURE 1) [4] with low TH activities.

In 1990, Fujita and Shintaku noticed decreased levels of neopterin and biopterin in the cerebrospinal fluid of a patient with HPD and suggested that the partial decrement of GCH-1, caused by abnormal pteridine metabolism, was the cause of HPD or Segawa disease (SD) [5]. Furukawa *et al.* observed the same abnormalities in the cerebrospinal fluid of four HPD cases and confirmed the cause of HPD to be partial deficiency of GCH-1 [6].

The development of pteridine metabolism also correlates with the age variation of the terminal TH [7]. Thus, this age variation in TH activity is considered to reflect the age variation in the activities of GCH-1. Therefore, the pathophysiology of HPD is speculated to be a nonprogressive decrement of the terminal TH or DA of the NSDA neuron caused by GCH-1 deficiency [1,8]. Pteridine metabolism develops during the late fetal period with a critical period in early infancy which extends to early childhood [7]. A study in stimulated mononuclear blood cells also showed an age-dependent decrement of the activities of GCH-1 in the first three decades of life [9]. Thus, pteridine metabolism may be involved in the age-related decrement of TH activity of the terminal of the NSDA neuron, particularly in its early phase [5].

In 1994, Ichinose *et al.* found the *GCH-1* gene and, by examination of seven Segawa patients, discovered a mutation in *GCH-1* located on chromosomes 14q22.1–q22.2 in four cases [10]. Although in three cases a mutation was not detected, these cases showed a marked decrease in the activities of GCH-1 in mononuclear blood cells [10]. Thus, SD was revealed to be caused by a *GCH-1* mutation [10].

Segawa had found two clinical types of cases of SD: a postural and action type [1,3]. The postural type starts with dystonic posture with rigidity in the lower extremity, mostly pes equinovarus, in children approximately 6 years of age, which expands to other limbs with age and involves all extremities and trunk muscle with rigidity occurring by the late teenage years. Along with these processes, postural tremor with a frequency of 8–10 Hz appears from approximately 10 years of age. However, dystonic posture with rigidity is the main symptom throughout the course of the illness.

Action type cases demonstrate dystonic movements of the limbs and trunk. For example, they show action retrocollis besides dystonic posture from approximately 8–10 years. Later, oculogyric crisis is associated. Furthermore, focal or

segmental dystonia appears after adolescence and parkinsonism appears in adulthood. In families with action type SD, there are cases that start with writer's cramp, torticollis or generalized rigid hypertonus with a postural tremor after adolescence or parkinsonism in adulthood.

Diurnal fluctuation suggests the effect of sleep for improvement of symptoms. To clarify this pathophysiology, we evaluated muscle activities during sleep by estimating two types of body movements: gross movements (GMs) involving muscles of the trunk and extremities; and twitch movements (TMs), characterized by short (<0.5 s) muscle activity restricted to one muscle. These parameters are evaluated by polysomnographies (PSGs) before and after L-dopa administration in both types [11,12].

In normal subjects, TMs in rapid eye movement (REM) sleep increase with sleep cycle and decrease with age. The degree of increment with sleep cycle reduces with age. The TMs of HPD patients followed these nocturnal and age variations, with lower levels of approximately 20% of normal values.

In the first cycle of REM sleep, TMs were markedly decreased to less than 20% of the levels of the last cycle of normal subjects, but in the last cycle, the levels exceeded more than 20% of it, which relates morning recovery [13].

Selective-stage REM deprivation abolished morning improvement, while selective slow-wave sleep deprivation did not affect morning improvement (stages III and IV). These were observed in both types [8]. Thus, REM sleep was demonstrated to involve diurnal fluctuation and TMs in REM sleep are shown to reflect the activities of the DA neuron [8]. After L-dopa was administered, the number of TMs were normalized in patients with both types of SD [8]. Polysomnographical studies on various basal ganglia disorders also demonstrated that the number of TMs in each REM stage reflects the activities of NSDA neurons [14]. It was also revealed abnormalities of the rate of occurrence of GMs against sleep stages in HPD (FIGURE 2).

The ratio of occurrence of GMs against the sleep stages, before L-dopa was administered, were found to be abnormal in both types. However, the ratio of occurrence of GMs against sleep stage after L-dopa administration showed a difference between the two types [8]. After L-dopa was administered, the pattern was normalized in the postural type, but in the action type it was not normalized and one case showed the pattern suggesting upward regulation of the DA D2 receptor, even though clinical symptoms were

Figure 1. Tyrosine hydroxylase activity in human striatum and substantia nigra as a function of age. (A) Age variation of the activities of TH in the caudate nucleus. **(B)** Age variation of the activities of TH in the substantia nigra. TH: Tyrosine hydroxylase. Reproduced with permission from [4].

normalized (FIGURE 2) [11,12]. Thus, at first, the action type was considered to be a different DRD from the postural type. However, all cases of the action type were shown to have a *GCH-1* mutation [15]. Thus, it is shown that SD has two clinical types. Each patient or family has a particular mutation for each, but there are no specific loci of mutations for postural and action type dystonia.

In both types of SD, the rate of growth decelerates with onset of dystonia in childhood, which extends to the levels of short stature in the midteenage years. Stagnation of body length is not observed in cases with an onset after midteenage years. This stagnation of body length also responds to L-dopa. Thus, administration of L-dopa by early teenage years improves the

Figure 2. The number of gross and twitch movements against the sleep stages in Segawa disease before and after L-dopa treatment. Postural type are the average scores of six cases. Action type are the results of two cases. GM: Gross movement; REM: Rapid eye movement; TM: Twitch movement. Reproduced with permission from [24].

stagnation of body length and the body length normalizes. However, L-dopa shows no effects on body length if administrated after a patient has reached their midteenage years.

Childhood-onset cases show marked female predominance; among the total of 41 cases, the ratio of male to female cases is 8:33. It is more marked in the postural type (1:18) than in the

action type (7:15); however, adult-onset cases show male predominance (5:1) [16]. Diurnal fluctuation of symptoms subsides in patients in their teenage years and disappears when a patient is in their mid twenties. Therefore, the diurnal fluctuation is not observed in cases with onset after adolescence.

Pathophysiology of SD

All of these symptoms show asymmetry as a characteristic feature of the basal ganglia disorders. However, the dominantly affected side of rigidity of the sternocleidomastoid and the extremities show differences between postural and action type. That is, it is contralateral in postural type but ipsilateral in action type [11]. Torticollis appearing during teenage years in patients with action type SD is ipsilateral to the dominantly involved side of the extremities.

In other basal ganglia disorders, the asymmetrical involvement is also observed in the sternocleidomastoid and extremities. In Parkinson's disease, the predominantly involved side of the sternocleidomastoid and the extremities is contralateral, while it is ipsilateral in DYT1.

This evidence indicates that the causative lesion of postural dystonia exists in the afferent structures of the striatum and that of action dystonia is located in the striatum or the downstream structures of the striatum. As both types of SD respond to L-dopa, for postural dystonia, involvement of NSDA neurons innervating the striatum is thought to be involved, and for action dystonia, involvement of NSDA neurons innervating the subthalamic nucleus (STN) is reported to be involved.

Furthermore, the side predominance of a postural tremor is ipsilateral between the sternocleidomastoid and the extremities in both types [11]. Therefore, for tremor, the NSDA neurons innervating the STN are considered to be involved in both types.

According to the rationale of movement disorders, a certain lesion causes a particular symptom or symptoms through the downstream structures, which are normal both in structure and function. Thus, in the developing brain, particular symptoms of movement disorders can appear after maturation of these neuronal structures.

McGeer and McGeer suggested the existence of two types of the NSDA neuron [4]. One engages DA transmission with high TH activities in the terminal, and the other with high TH activities in the perikaryon. The TH activities of both types show particular developmental courses for each (FIGURE 1) [4]. The former shows high TH activities in the terminal in early childhood,

which decreases exponentially with age and reaches basement levels by the time the patient reaches their early twenties. On the other hand, the TH activity in the perikaryon or the substantia nigra (SN) increases linearly with advancing age from late childhood [4]. Thus, the former has main roles in DA transmission in childhood and the latter takes over these roles from the mid-teenage years. Furthermore, diurnal fluctuation of the activity is observed in the terminal TH, but TH or DA in the perikaryon does not show state-dependent alternation [4,17].

Developmental courses of the direct and the indirect pathways of the basal ganglia are shown in the development of the parameters of voluntary saccades [14]. Visually guided saccade is modulated through the direct pathway of the basal ganglia and its parameters mature by 6 years, while parameters for memory-guided saccade, which are involved in the indirect pathway, attain maturational levels at approximately 15 years of age [14]. As discussed previously, the STN matures early in childhood [11,18]. As for the output pathways of the basal ganglia, descending pathways mature earlier in early childhood, while the ascending pathways mature later in the midteenage years.

The study of an autopsied case of SD revealed decrease of TH in the striatum, while TH levels remained stable in the SN [19]. Furthermore, the area of DA depletion in the striatum was predominant in the ventral area [19]. This is in contrast to the dorsal area predominance in Parkinson's disease. This implicates the predominant involvement of the striosome in the striatum in SD, which is rich in D1 receptors. Thus, in SD, TH or DA deficiency in the striatum causes dysfunction of the D1 direct pathway, which is located in the ventral area of the striatum and matures earlier among DA receptors.

In SD, administration of L-dopa is necessary, even though the DA activity in the pars compacta of the SN are preserved. This confirmed the presence of two NSDA neurons, each of which has particular neuronal connections to the pathways of the basal ganglia.

Deficiency of GCH-1 may cause a deficiency of tryptophan hydroxylase (TPH) with TH. However, the K_m value of TH for GCH-1 is higher than TPH. As SD is caused by a heterozygous mutation in *GCH-1*, the deficiency of GCH-1 is partial. Thus, TH is affected rather selectively in SD [11].

Thus, the pathophysiology of SD is considered as follows. For postural dystonia with an onset in childhood, the NSDA neuron with high TH

Figure 3. Genomic structure and location of mutations in the human *GCH-1* gene (chromosomes 14q22.1–q22.2).

bp: Base pair; E: Exon.

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activities in the terminals is involved. A decrease of TH in the terminal causes disfacilitations of D1 receptors of the direct pathway and consequently disinhibits the GABAergic neuron, consisting of the descending output of the basal ganglia, and induces postural dystonia. On the other hand, in action dystonia with onset at approximately 10 years, the NSDA neuron innervates the STN. Dysfunction of this neuron causes disfacilitation of the STN and consequently

disfacilitates the output of GABAergic neurons of the basal ganglia. This causes action dystonia through the descending output pathway in late childhood and focal or segmental dystonia or parkinsonism through the ascending pathway of the basal ganglia during teenage years, particularly after adolescence with functional maturation of the ascending pathways. Furthermore, this difference in pathophysiology clarifies that postural dystonia is a hypokinetic disorder and action

dystonia is a hyperkinetic disorder. The pattern of PSG in action type SD correlates with the pattern observed in patients with upward regulation of the DA receptor, which demonstrates the pathophysiology of a hyperkinetic disorder [11].

However, in early-onset cases and cases with compound heterozygosity, decrement of GCH-1 is more marked and causes deficiency of 5-HT with TH. Thus, in these cases, symptoms caused by 5-HT deficiency – that is, hypotonia, failure in locomotion caused by deficiency of antigravity activities and psychobehavioral disorders, such as depression, are observed. Moreover, insufficiency of the antigravity activity causes a failure to restrict atonia in the REM stage. This induces dysfunction of the pedunculopontine nucleus and consequently causes dysfunction of the DA in the pars compacta of the SN and the ventro- tegmental area. In these cases, upward regulation of the DA receptors may occur, thus inducing dyskinesia with L-dopa. These processes are not observed in postural type SD with normal locomotion [18]. For treatment of these cases, administration of tetrahydrobiopterin as well as L-dopa is necessary.

As for the stagnation of body length, the tuberoinfundibular DA neuron with the D4 receptor may be involved. The D4 receptor belongs to the D2 receptor group, which matures later. However, the D4 receptor is shown to mature early [20]; thus, its dysfunction can cause clinical symptoms in childhood. Therefore, stagnation of body length is caused by deficiency of TH of the tuberoinfundibular DA neuron projecting to the pituitary gland with D4 receptor [11]. This neuron is active from childhood to early teenage years and becomes silent after the cessation of

the growing process. Thus, stagnation of body length is not observed in cases with SD onset after midteenage years.

The loci of mutation & clinical characteristics

As for the pathogenetic mechanisms for dominant inheritance with a heterozygous mutation, classic dominant-negative effects have been considered [11,13]. The rates of mutant *GCH-1* mRNA production against normal mRNA were 28% in one patient, but 8.3% in an asymptomatic carrier [11,13]. However, the ratio varies depending on the locus of the mutation. Furthermore, the ratio differs among affected individuals in some families. These may cause inter- and intra-familial variation of the phenotype, as well as the rate of penetrance. Furthermore, the loci of the mutation may also be involved in determining the phenotype.

The loci of mutations *GCH-1* of DRD, including personal cases, are shown in FIGURE 3. In FIGURE 4, mutations of Segawa's personal cases separating postural type and action type are shown. Each patient or family has a particular mutation. However, the IVS3+IG>A mutation was observed in two nonrelated families, one with postural type and the other with action type. All mutations are reported from different families in Japan. The gene Gly203Arg, which was observed in an action type case, was also observed in Korean and Taiwanese families. Bandmann *et al.* detected other mutations, such as Leu71Glu, Ala74Val, Gly83Ala, Val191Ile, Met211Val and Arg224Trp, which were observed in families from various countries [21]. Therefore, there are no particular loci for postural and action type dystonia.

Figure 4. Locus of the mutations: postural type and action type of *GCH-1* deficiency of author's cases.

E: Exon.

Adapted with permission from [25].

Furukawa *et al.* showed a marked reduction of total bipterin (84%) and neopterin (62%) in the putamen, despite a normal concentration of aromatic acid decarboxylase, DA transporter and vesicular monoamine transporter [22]. These authors also demonstrated modest reduction of the TH protein (52%) and DA (44%), despite marked reduction of striatal bipterin (82%) in an asymptomatic carrier, and implicated the levels of TH protein as a key for the development of symptoms [23]. The activities of GCH-1 in the mononuclear blood cells decreased to less than 20% of normal levels in patients and 30–40% in asymptomatic carriers [10]. Thus, it has not been clarified why certain mutations in *GCH-1* cause these disorders with different pathophysiologies and why the mutation causes a difference in the grade of dysfunction of GCH-1.

However, molecular analysis remains unable to determine mutations in the coding region of

the gene in approximately 40% of subjects with *GCH-1* deficiency. In these cases, abnormalities in intron genomic deletion, a large gene deletion, an intragenic duplication or inversion of *GCH-1* or mutation in as yet undefined regulatory gene-modifying enzyme function may be present [11].

In TABLES 1 & 2, postural type (TABLE 1) and action type (TABLE 2) of Segawa's personal cases are shown, where L-dopa was administered for more than 15 years. The initial dose of plain L-dopa was 2–5 mg/kg/day and the maximum or treatment dose was 20 mg/kg/day. As for carbidopa, one-fourth or one-fifth doses of plain L-dopa were administered. In cases that started with plain L-dopa administration in childhood, the effect decreased in early teenage years and it was necessary to administer carbidopa. This is thought to be due to activation of decarboxylase in the intestine, which begins in this age period. However,

Table 1. Patients of postural type with long-term treatment.

Patient	Gender	Loci of mutation	Mutation	Age of onset	Initial symptom	Age at L-dopa administration [†]	Age at last exam (years)	Phenotypical variation	Familial occurrence
P-1	Female	Exon 1	3insGG	7 years	Pes equinovarus	10 years 8 months	41	–	+ Mother
P-2	Female	Exon 1	3insGG	9.5 years	Gait disturbance	39 years 11 months	68	–	+ Daughter
P-3	Female	Exon 1	Leu79Pro	4 years	Pes equinovarus	34 years 8 months	68	Depression	–
P-4	Female	Exon 1	Arg88Trp	5 years 1 month	Abn. standing posture pes equinovarus	5 years 7 months	31	–	–
P-5	Female	Exon 2	Asp134Val	1 year 4 months	Talipes equinus	3 years 11 months	48	–	+ Grandmother and cousin
P-6	Female	Exon 2	Asp134Val	8 years	Pes equinovarus	51 years	91 (died of cancer)	–	+ Granddaughter and nephew
P-7	Male	Exon 2	Asp134Val	3 years	Gait disturbance	10 years	51	–	+ Aunt and niece
P-8	Female	Intron 3	IVS3+1G>A	8 years 5 months	Right pes equinovarus	8 years 11 months	54	Migraine	+ Relatives
P-9	Female	Intron 3	IVS3+1G>A	4 years	Left pes equinovarus	6 years	51	–	+ Relatives
P-10	Female	Intron 3	IVS3+1G>A	10 years	Pes equinovarus	15 years 2 months	43	Headache	+ Cousin
P-11	Female	Exon 4	511del13bp	7 years	Left pes equinovarus	9 years 6 months	44	–	–
P-12	Male	Exon 5	Gly201Glu	8 years	Right upper extremity	11 years	54	Dysarthria	+ Aunt
P-13	Female	Intron 5	IVS5+1G>A	9 years	Left pes equinovarus	11 years 9 months	27	Headache	+ Mother-side second cousin

[†]Starting age of L-dopa administration at the author's clinic.

+: Presence of Segawa disease in family members; Abn.: Abnormality; P: Postural type.

Table 2. Patients of action type with long-term treatment.

Patient	Gender	Loci of mutation	Mutation	Age of onset	Initial symptom	Age at L-dopa administration [†]	Age at last exam (years)	Phenotypical variation	Familial occurrence
A-1	Male	Exon 1	200ins4bp	8 years	–	13 years	37	–	+ Father and sister
A-2	Female	Exon 2	Cys141Arg	6 years	Left pes equinovarus	12 years 11 months	35	Trunk dorsiflexion torticollis	+ Father
A-3	Female	Exon 2	Cys141Arg	10 years	Right pes equinovarus	38 years 8 months	56	Headache Psychosis	+ Mother
A-4	Female	Exon 2	Cys141Arg	7 years 6 months	Gait disturbance	38 years 8 months	55	–	+ Father
A-5	Female	Exon 2	Cys141Arg	10 years	Left pes equinovarus	15 years 6 months	31	–	+ Mother
A-6	Female	Intron 3	IVS3del+1-+4	7 years	Gait disturbance	11 years 8 months	43	–	+ Father
A-7	Male	Intron 3	IVS3del+1-+4	55 years	Hand tremor	57 years 10 months	73	–	+ Daughter
A-8	Female	Exon 4	Gln180Stop	8 years	Right pes equinovarus	10 years 1 month	41	–	+ Sister
A-9	Female	Exon 5	547insG	7 years	Gait disturbance with pain	12 years	51	Writers cramp	+ Daughter
A-10	Female	Exon 5	547insG	10 years 8 months	Gait disturbance	11 years 6 months	27	–	+ Mother
A-11	Female	Exon 5	Gly203Arg	5 years	Left pes equinovarus	20 years	43	Writers cramp	+ Son
A-12	Female	Exon 6	Met230Ile	7 years	Gait disturbance	36 years	51	Torticollis	+ Siblings

[†]Starting age of L-dopa administration at the author's clinic.

+: Presence of Segawa disease in family members; A: Action type.

there were cases that responded to plain L-dopa throughout the course of the illness. In all cases, L-dopa demonstrated favorable effects without any relation to the ages at onset, longevity of nontreatment course and ages at which L-dopa was started. Although one case of action type SD showed dyskinetic movement with an initial administration of L-dopa, it disappeared by starting with smaller doses after stopping the initial dose.

Cases with onset before 2 years demonstrated hypotonia, failure in locomotion, depression and mild mental retardation as well as dystonia. These symptoms are considered to be caused by 5-HT deficiency, which occurred due to marked deficiency of GCH-1. In such cases, administration of the hydroxytryptophan, in addition to L-dopa, is necessary.

Conclusion

HPD, or SD, is an autosomal-dominant DRD caused by a heterozygous abnormality of the

GCH-1 gene. As the deficiency of GCH-1 is partially due to a heterozygous deficiency, TH with higher K_m values to GCH-1 than TPH is affected rather selectively. As HPD occurs in childhood, among the DA neurons and the structures of the basal ganglia those develop earlier in childhood are involved in its pathophysiology.

Thus, among the NSDA neurons, one modulating neural transmission with high TH activity in the striatal terminal and the other projecting STN, which mature early in childhood compared with other structures of the indirect pathway, are involved. As for the neuronal pathways of the basal ganglia, the direct pathway and descending pathways, which mature early in childhood, are involved, but the ascending pathways are only involved in the pathophysiology of a SD patient in their teenage years, mainly after their midteenage years.

Clinically, HPD is classified into two types; postural type and action type. The postural type

is caused by dysfunction of the TH in the striatal terminal of the NSDA neuron, while for the action type the NSDA neuron projecting to the STN is involved. This neuron is also considered to be involved in tremors.

Cases of action dystonia develop dystonic movement beside dystonic posture from approximately 10 years of age and show focal or segmental dystonia in teenage years. For these, the NSDA neuron innervating to the STN is considered to be involved. Furthermore, in families of the action dystonia, there are cases starting with focal or segmental dystonia after adolescent and parkinsonism in adulthood with maturation of the ascending pathway of the basal ganglia. For postural tremor, the NSDA neuron innervating to the STN is considered to be involved.

In both types, cases that occur during infancy or early childhood show symptoms caused by a deficiency in 5-HT. Furthermore, these cases have dysfunction of the pedunculopontine nucleus, which consequently causes dysfunction of DA in the SN and the ventro tegmental area. HPD shows marked female predominance; however, cases with onset in adulthood show male predominance.

To date, more than 100 mutations have been detected and each family or sporadic case has had a particular mutation. However, it has not been clarified why certain mutations cause either postural or action type SD, why certain mutations cause symptomatic or asymptomatic cases and why certain mutations cause symptoms in particular ages of years with gender difference.

Future perspective

During the next decade, the following investigations will be necessary:

- To clarify why certain mutations in *GCH-1* cause these disorders with different pathophysiology in certain ages;
- To clarify or to identify the descending and the ascending output pathways of the basal ganglia, whether they are involved by the direct pathway, or by the indirect pathways;
- To identify the pathways in the basal ganglia and output pathway of the the basal ganglia, whether they are modulated by the NSDA neuron with high TH activities in the terminal or modulated by the NSDA neuron with high TH activities in the SN. Furthermore, to identify the pathway modulated by the NSDA neuron innervating the STN;
- To clarify the developmental course of the NSDA neurons projecting to the STN;
- To identify whether the basal ganglia outputs are identical or different, which are modulated by the NSDA neuron projecting to the D2 indirect pathway and to the STN;
- To clarify the maturational courses of the D1 direct pathway, the D2 indirect pathway and their output pathways;
- To clarify the pathogenesis why the *GCH-1* mutations cause various grades of symptoms and disorders of various pathophysiologies.

Executive summary

- Segawa disease is caused by mutations or abnormalities in the *GCH-1* gene, which is located on chromosomes 14q22.1–q22.2.
- More than 100 mutations and abnormalities in the *GCH-1* gene are detected in patients with dopa-responsive dystonia, which is characteristic of Segawa disease.
- Segawa disease has two clinical types: postural type and action type.
- In both types, tyrosine hydroxylase (TH) is selectively involved in the terminal.
- There are no particular mutations for each clinical type. Each case of both types has a particular mutation or an abnormality of the gene.
- There are two types of nigrostriatal dopamine (NSDA) neurons. One modulates neuronal transmission with high TH in the terminal, and the other with high TH in the perikaryon.
- The two types of the NSDA neurons innervate the striatum.
- Beside them, there is another NSDA neuron that projects to the subthalamic nucleus, which may have high TH activities in the terminal.
- The terminal TH is synthesized by *GCH-1*.
- For the synthesis of the perikaryon TH, *GCH-1* is not involved, but the pedunculopontine nucleus is involved in its synthesis.
- These three NSDA neurons have particular developmental courses and roles in dopamine transmission for each.
- The structures for each pathway in the basal ganglia and descending and ascending output pathways of the basal ganglia are considered to have particular developmental courses.
- There are gender difference in the NSDA neurons.
- Diurnal fluctuation is only observed in the NSDA neuron with high TH activities in the terminal.

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▪ of interest

▪▪ of considerable interest

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The genetics of Segawa disease

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 13-year-old girl thought to have possible hereditary progressive dystonia (HPD). Based on the review by Dr. Segawa, which of the following statements about the clinical characteristics and course of Segawa disease is **most likely** correct?

- ☐ A In the postural type, dystonic posture is a predominant symptom throughout the course of the illness
- ☐ B In the action type, focal or segmental dystonia begins in early childhood
- ☐ C Segawa disease is not responsive to L-dopa
- ☐ D Short stature for age has not been reported

2. Based on the review by Dr. Segawa, which of the following statements about the genetics of Segawa disease is **most likely** correct?

- ☐ A To date, 10 mutations of the GTP-cyclohydrolase 1 (GCH-1) gene have been identified
- ☐ B Postural cases have a specific genetic mutation different from action cases
- ☐ C Inheritance is recessive
- ☐ D Segawa disease is caused by abnormalities of the GCH-1 gene located on 14q22.1 to q22.2

3. Based on the review by Dr. Segawa, which of the following statements about the neurophysiology underlying HPD would most likely be correct?

- ☐ **A** The postural type, but not the action type, is associated with symptoms of dopamine deficiency
- ☐ **B** *GCH-1* deficiency causes deficiency of tyrosine hydroxylase (TH) in nigrostriatal dopamine (NS-DA) neuron terminals
- ☐ **C** There are 4 main types of NS neurons involved in HPD
- ☐ **D** *GCH-1* is involved in TH synthesis in the perikaryon