

Dopa-Responsive Dystonia Is Caused by Particular Impairment of Nigrostriatal Dopamine Neurons Different from Those Involved in Parkinson Disease: Evidence Observed in Studies on Segawa Disease

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Abstract

From the characteristics of its clinical features, Segawa disease is considered to be caused by deficiency of the tyrosine hydroxylase (TH) of the nigrostriatal dopamine neurons, which have high TH activities in the terminal but not in the perikaryon. This hypothesis was confirmed by two autopsied cases. However, these cases were younger than 40 years and left a question as to whether these abnormalities turned to those of Parkinson disease in older ages. An autopsy of a 90-year-old woman with Segawa disease confirmed the hypothesis that Segawa disease has a completely different pathophysiology and pathology than Parkinson disease.

Keywords

- ▶ Segawa disease
- ▶ Parkinson disease
- ▶ nigrostriatal dopamine neuron

Introduction

Segawa disease is an autosomal dominant dopa-responsive dystonia caused by abnormality of the guanosine triphosphate (GTP) cyclohydrolase 1 (GCH-1) gene located on 14q22.1-q22.2. GTP is involved in the synthesis of tetrahydrobiopterin (BH₄), the cofactor of tyrosine hydroxylase (TH), a crucial step in dopamine production. This hypothesis was supported by neurohistochemical findings observed in two autopsied patients with Segawa disease, which showed dopamine deficiency in the terminals of the nigrostriatal dopamine neuron but preservation of dopamine in the pars compacta of the substantia nigra. These results suggested that Segawa disease is different from Parkinson disease. However, these autopsied cases were younger than 40 years of age. We questioned if the pathologies of Parkinson disease might appear in individuals with Segawa disease in patients older than 60 or 70 years of age. We here report on brain autopsy findings of a 90-year-old woman with confirmed Segawa disease.

Clinical Characteristics of Segawa Disease

Clinically Segawa disease is divided into two types, a postural type and an action type, depending on the loci of mutation of the GCH-1 gene.¹

The postural type starts with dystonic posture of one leg, mostly pes equinovarus, around the age of 6 years. The dystonia expands to other extremities and the trunk with age, and by the teenage years all extremities are involved. Dystonia is based on rigid muscular hypertonus. These symptoms show marked diurnal fluctuation. Besides these, postural tremor appears from around 10 years of age in one upper extremity with diurnal fluctuation, which expands to other extremities and neck muscles with age. However, the grade of progression of these symptoms attenuates with age, and in the third decade all symptoms become stationary. Along this process, the grade of diurnal fluctuation reduces, and in the third decade fluctuation becomes unremarkable.

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In the action type, besides postural dystonia, dystonic movements appear from around 8 to 10 years of age. These are observed in the upper extremities and also in the neck muscles as action torticollis. Postural dystonia shows a similar clinical course as that of the postural type, but the progression of the action dystonia is quite discrete. However, some of these patients show segmental or focal dystonia such as torticollis or writer's cramp from adolescence. Furthermore, there are individuals within families affected by the action type whose disease onset occurs in adolescence to adulthood as torticollis or writer's cramp and in late adulthood with generalized rigidity and postural tremor—that is, parkinsonism.

In both types, increased muscle tone is due to rigidity; cogwheel signs are absent, though postural tremor exists. Deep tendon reflexes are exaggerated and some show ankle clonus, but pyramidal tract signs are not observed. There are no psychomotor abnormalities.

In both types, all symptoms show asymmetry. However, the side predominantly involved in the sternocleidomastoideus (SCM) and in the extremities differs among symptoms and also between the postural type and the action type. As for muscle rigidity, the side predominantly involved is contralateral in the postural type, whereas it is ipsilateral in the action type. Thus, torticollis appears on the side of the extremity with predominant involvement of the rigidity. However, for tremor it is ipsilateral in both types. This suggests that for the muscle rigidity of the postural type, the causative lesion is in the afferent structures of the striatum—that is, the nigrostriatal (NS) dopamine (DA) neuron. On the contrary, for the rigidity of the action type and the postural tremor of both types, the causative lesion is in the striatum or the structures downstream of it. As these symptoms are responsive to L-dopa, the involvement of the nigrostriatal-dopaminergic (NS-DA) neuron projecting to the subthalamic nucleus (STN), which was shown by Kreiss and his colleagues,^{2,3} is implicated.

Pathophysiologies of Segawa Disease

According to the basic pathophysiology of the movement disorders, the causative lesion develops symptoms through the downstream structures, which are structurally and functionally normal. In Segawa disease, all symptoms appear before 10 years of age. Thus, neural systems that have matured structurally and functionally before age 10 should be involved. According to McGeer and McGeer,⁴ activities of the TH of the NS-DA neurons show age variation between the terminal and the perikaryon. The TH activities in the terminal are high in early childhood and exponentially decrease toward the early teens, attaining basement levels in the twenties. In contrast, TH activities in the perikaryon are low in childhood and increase linearly with age, exceeding the levels of the terminal in the late teens. This suggests that, in childhood, the terminal TH has the main roles in DA transmission, whereas in the teens this is taken over by the perikaryon. The terminal TH is known to have diurnal fluctuation, whereas the perikaryon TH does not show state-dependent variation.⁴ The direct pathway of the basal ganglia matures early, and the indirect pathway matures later.⁵ The

output pathways of the basal ganglia descending pathways mature in childhood, and the ascending pathways mature later, in the midteens.⁶

As patients with Segawa disease develop symptoms in childhood with marked diurnal fluctuation, decrease of the TH in the terminal is considered as the underlying cause. Thus, the postural dystonia is caused by deficiency of TH in the terminal of the NS-DA neuron projecting to the DA D₁ receptor on the direct pathways. This impairs the direct pathway and, by disinhibiting the descending pathway of the basal ganglia, induces postural dystonia. As the indirect pathways of the basal ganglia are functionally immature before 15 years of age,^{6,7} the DA D₂ receptors are not involved in the clinical symptoms of Segawa disease. However, among the structures of the indirect pathway, the STN matures in early childhood³ and its dysfunction can cause symptoms in childhood. Kreiss et al^{2,3} showed that the DA neuron mediates STN via the D₁ receptor located on the nucleus. Thus, in action dystonia, hypofunction of the TH in the terminals of the NS-DA neuron projecting to the STN causes dysfacilitation (impairment) of the STN, which by dysfacilitation of the output pathways of the basal ganglia induces action dystonia through the descending pathway and torticollis, writer's cramp, and parkinsonism through the ascending pathway. Furthermore, these pathophysiologies show that symptoms caused by the D₁ direct pathway are hypokinetic disorder, and those caused by the STN are hyperkinetic disorders.

Two autopsies with neurohistochemical studies of the brain were conducted of patients with Segawa disease—an 18-year-old woman who died by traffic accident^{8,9} and a 39-year-old woman who died of paralytic illness.¹⁰ The latter was reported as juvenile parkinsonism¹⁰ but was later reclassified as Segawa disease on the basis of reanalyzing clinical symptoms and identifying her brother as adult-onset Segawa disease.¹¹ According to clinical features, the 18-year-old patient was considered to have the postural type and the 90-year-old patient the action type.¹¹ Neurohistochemical studies on both cases showed a decrease of DA or TH in the striatum, and the activities of DA or TH in the perikaryon or the substantia nigra were not affected.^{8,11} In the 18-year-old patient's case, DA loss was more prominent in the striosomes/patches compartment, the terminal for the D₁ receptor^{8,9} and (in contrast to Parkinson disease) showed a greater DA loss in the ventral subdivision of the rostral caudate than its dorsal counterpart.⁸ These findings support decrease of the TH in the terminals of the NS-DA neuron in Segawa disease. However, as both patients were younger than 40 years, the remaining question was whether these pathophysiologies turned into those of Parkinson disease in older ages. A brain autopsy of one patient with Segawa disease that died at the age of 90 years helped to clarify this issue.

Clinical Features and Neuropathological Findings of the Case

This 90-year-old woman was the paternal grandmother of the proband of a family with the postural type of Segawa disease (►Fig. 1). One of her nephews also had Segawa

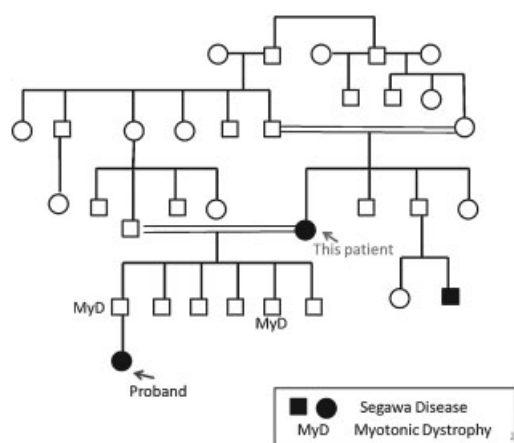


Fig. 1 Pedigree of the 90-year-old case.

disease. The pregnancy course and developmental courses in infancy and early childhood were noncontributory, and there were no abnormalities in motor and psychomotor development. Initial symptoms appeared around 8 years with pes varus on the left, which aggravated toward the evening. The symptoms showed progression, and in the early teens she could not walk except in the morning. With the expansion of dystonic postures, muscle hypertonus exacerbated with age, particularly in her teens. In her early teens, fine tremulous movements appeared on the upper extremities, particularly on her left thumbs, and expanded to all extremities and trunk muscles by her late teens to early twenties. Gait disturbance was aggravated within her teenage years. However, all symptoms became stationary from her midtwenties. At the age of 19 years, she was married, and the first confinement was at 21 years. She delivered a total of six children; pregnancy and delivery did not affect her neurological symptoms.

She visited our clinic at the age of 51 years. Neurological examination revealed postural dystonia, with pes varus and pronation of the elbow, rigidity of the extremities, bradykinetic pronation/supination, and mild postural tremors of both hands. These symptoms showed left-side predominance. The corticospinal tract, cerebellum, and sensory system were preserved. There was mild lordosis and scoliosis concave to the left. There was no psychomotor abnormality. Gene analyses showed a mutation of Asp134Val in

exon 2 of the GCH1 gene, the same as observed in her granddaughter. Compound L-dopa was started from the age of 51 years. At first, mild dysknetic movements appeared, but this was transient and 100 mg per day, divided into two dosages, showed favorable effects that continued without any side effects until age 90.

Neuropathological and immunohistochemical Examination of This Case

She died of malignant lymphoma lung cancer at the age of 90 years 6 months. Her brain was autopsied, and neuropathological and immunohistochemical investigations of the brain were performed at Tokyo Metropolitan Institute of Medical Science. Brain weight was 960 g, within age-compatible controls. No anomalous lesions nor atrophy were observed (►Fig. 2A, B). The bilateral olfactory bulb and tracts, optical chiasm, pituitary stalk, bilateral mammillary bodies, and cranial nerves were identified. Mild to moderate atherosclerosis was found in the arteries consisting of the circle of Willis. The folia formation, pontine base, and medullary pyramis were all preserved. Routine histochemistry revealed no abnormalities except cell loss and fibrillary gliosis of the nucleus parafascicularis of the thalamus. The results of immunohistochemical examinations revealed findings are shown in ►Table 1. These findings confirmed the hypothesis that Segawa disease is caused by deficiency of TH in the terminals of the NS-DA neuron with high TH activities in the terminal and is a different disorder from Parkinson disease.

Discussion

The clinical course of this 90-year-old woman is well explained by following the age-dependent decremental course of the TH in the terminal of the NS-DA neuron shown by McGeer and McGeer,⁴ with the levels of TH around 20% of normal without progressive decrement (►Fig. 6). The findings of immunohistochemical studies on the autopsied brain confirmed this speculation. Furthermore, the necessity L-Dopa administration in state with normal TH activities in the substantia nigra suggests the existence of two NS-DA neurons—that is, the presence of a particular nigrostriatal DA neuron, for dystonia of Segawa disease besides that for Parkinson disease. The NS-DA neuron involved in Segawa

Table 1 Neuropathological and immunohistochemical findings

Definite decrease of tyrosine hydroxylase (TH) in the calbindin-D28k-negative striosome in the lateral region of the putamen, while TH activities in the substantia nigra preserved normally (►Fig. 3).
Calcineurin in the projection neurons and DA D ₂ receptor in the putamen were preserved (►Fig. 4).
The enkephalin levels in the external segment of the globus pallidus were preserved
Substantia nigra had age compatible melanin pigmentation (►Fig. 5).
There were no inclusions such as Lewy bodies in either hematoxylin and eosin staining or antiphosphorylated α -synuclein immunostaining in the substantia nigra.
In the pedunculopontine tegmental nucleus, acetylcholine neurons and immunoreactivity for acetylcholine esterase were reduced, and TH-immunoreactive catecholamine neurons and CD-immunoreactive GABAergic neurons were increased. These findings may be age-related changes.

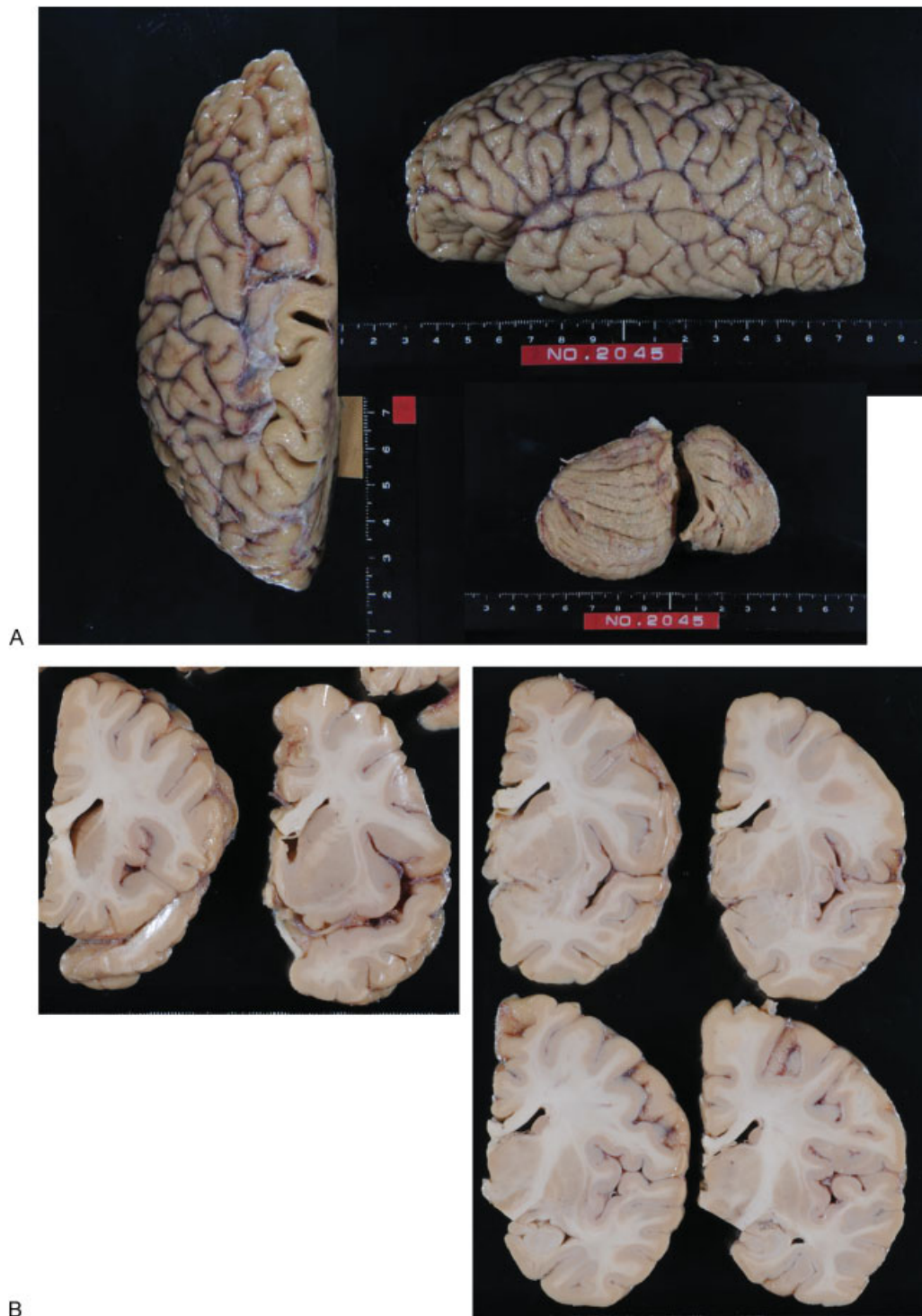


Fig. 2 A, Macroscopic features of the left cerebrum and cerebellum. B, Cross-sections of the left cerebrum demonstrated no morphological changes. The bilateral olfactory bulb and tracts, optical chiasm, pituitary stalk, bilateral mammillary bodies, and cranial nerves were identified. Mild to moderate atherosclerosis was found in the arteries consisting of the circle of Willis. The folia formation, pontine base, and medullary pyramis were all preserved.

disease is that which modulates DA transmission with high TH or DA activities in the terminals. Considering the age-dependent decremental variation of these activities, this NS-DA neuron has roles in DA transmission in childhood and has diurnal fluctuation. However, considering the pathophysiological and pathological findings of Segawa disease, this

neuron does not modulate function or structures of the DA receptors, nor the function or structure of the cortex, and it finishes its role in the early twenties. Considering its relation to dystonia, this neuron might modulate striated muscles that are not usually used voluntarily and regulate reciprocal activities of the agonistic and antagonistic muscles. The TH

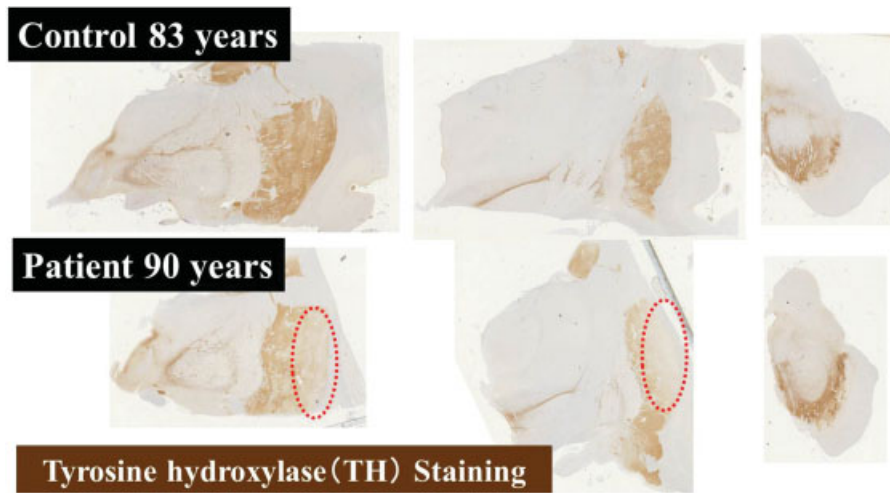


Fig. 3 Immunohistochemistry for tyrosine hydroxylase (TH) in the 83-year-old control (upper illustrations) and the case (lower ones). Immunoreactivity for TH in the putamen was reduced in the case, although that in substantia nigra was well preserved.

or DA activities of this neuron are modulated by pteridine and TH metabolism.

The other NS-DA neuron is involved in Parkinson disease. This neuron modulates DA transmission with DA activities in the perikaryon—that is, the substantia nigra pars compacta (SNc). The activities are low in childhood. Increasing the levels of activities linearly with age, this NS-DA neuron begins to share roles in neuronal transmission from the midteens. Failure of this NS-DA neuron causes Parkinson disease in adulthood. The DA activities of the perikaryon are not modulated by pteridine metabolism nor by TH metabolism.

Marked deficiency of TH in the SNc is observed in Rett syndrome (RTT),¹² which develops parkinsonism from

around 30 years of age. RTT has dysfunction of the aminergic neurons involved in modulation of antigravity activity, which is shown by leak out of atonia of rapid eye movement (REM) stage into non-REM stages.¹³ In RTT, components of REM stage are preserved. Thus, the activities of TH in the SNc are considered to be modulated by the pedunculopontine nucleus, the activities of which are modulated by the serotonin and the noradrenaline neurons involved in activation of the postural tone and locomotion and restrict atonia in REM stage. Considering the pathophysiologies and neuropathologies of RTT, the NS-DA neuron with high TH activities in the SNc has roles in modulating receptors and the higher cortical function in the developing brain. This neuron may also be

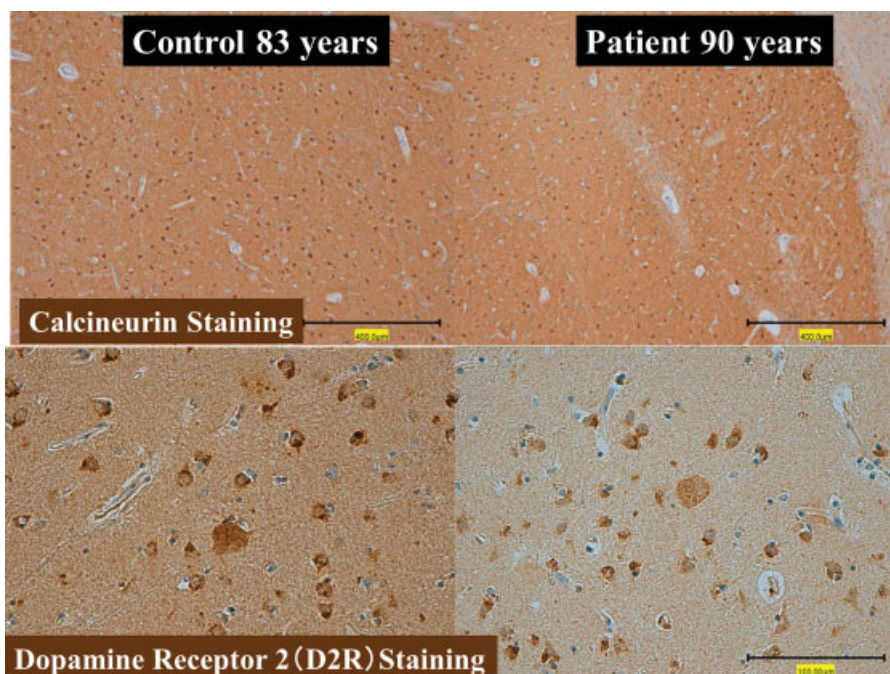


Fig. 4 Immunohistochemistry for calcineurin (upper illustrations) and dopamine receptor 2 (DAR2) (lower ones) in the 83-year-old control and the case. Immunoreactivity for both calcineurin and DAR2 in the putamen calcineurin and DAR2 in the putamen was well preserved in the case.

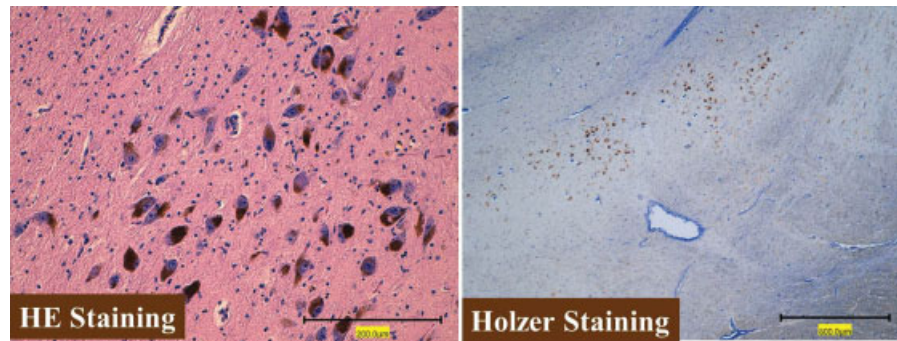


Fig. 5 Substantia nigra showed neither neuronal loss (HE staining) nor gliosis (Holzer staining).

Age Variation of the Tyrosine Hydroxylase Activities of the Caudate Nucleus Versus the Clinical Course of Segawa Disease

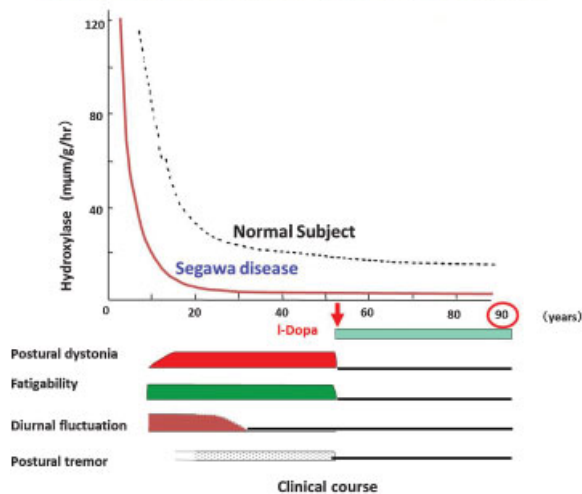


Fig. 6 Age variation of the tyrosine hydroxylase activities of the caudate nucleus vs the clinical course of Segawa disease.

involved in morphogenesis of the neuronal structures. Thus, in childhood—particularly in the developing brain—this neuron has important roles in the functional and morphological development of the central nervous system, particularly of the frontal cortex, but does not have marked roles in motor function in these ages. Thus, these two NS-DA neurons with different developmental course have particular, age-dependent roles in DA transmission and function of the central nervous system in the developing brain.

Conclusion

The pathophysiology of Segawa disease is confirmed by an autopsied brain of a 90-year-old woman. It revealed the cause of the disease as deficiency of the activities of the NS-DA neuron that modulates dopamine transmission with high TH activities in the terminals of the neuron. This differs from the pathophysiology of Parkinson disease, which is caused by deficiency of dopamine in the substantia nigra pars compacta of the NS-DA neuron. The NS-DA neuron with high TH activities in the terminal might also be involved in the pathogenesis of dopa-responsive dystonia with onset in childhood. This evidence suggests that there are particular

NS-DA neurons with particular age-dependent roles. Similar conditions should exist in other aminergic neurons that clinically show age-dependent change and have roles in the morphological and functional development of the central nervous system.

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