

Autosomal Dominant GTP Cyclohydrolase I (AD GCH 1) Deficiency (Segawa Disease, Dystonia 5; DYT 5)

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Autosomal dominant GTP cyclohydrolase I (AD GCH 1) deficiency (Segawa disease) is an autosomal dominant dopa responsive dystonia caused by heterozygous mutation of the GCH 1 gene located on 14q22.1-q22.2. Although a number of mutations have been reported, the change remains highly stable within families, and causes a decrease in the tyrosine hydroxylase protein at the nigrostriatal (NS)-dopamine (DA) neuron terminal. In addition, decreased tetrahydrobiopterin levels early in the development affect DA receptors age-dependently, and produce a spectrum of specific symptoms attributed to neuronal changes traced to processes in the development of the NS-DA neuron, related striatal projection neurons, and the output projection of the basal ganglia. (*Chang Gung Med J* 2009;32:1-11)



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Key words: Segawa disease, postural dystonia, action dystonia, GTP cyclohydrolase I, dopa responsive dystonia

Definition and classification

Autosomal dominant (AD) GTP cyclohydrolase I (GCH 1) deficiency or Segawa disease is a dopa responsive dystonia (DRD) caused by heterozygous mutation of the GCH 1 gene, located on chromosome 14q22.1 to q22.2.⁽¹⁾ This disease was called 'hereditary progressive basal ganglia disease' in case reports of two girls who were cousins.⁽²⁾ But after experience with an adult case with a 43 year clinical course, this disease was confirmed as dystonia and was published under the name 'hereditary progressive dystonia with marked diurnal fluctuation (HPD)'.⁽³⁾ Prior to identification of the causative gene of HPD, this disease was called Segawa syndrome,⁽⁴⁾ including the recessive type, which was later clari-

fied as recessive tyrosine hydroxylase (TH) deficiency. In the 1990s, it was also called DRD.^(5,6) Recently it was classified as DYT 5 with recessive TH deficiency or was called Segawa disease. In this paper, I review the clinical characteristics, laboratory findings and pathophysiology.

Clinical signs and symptoms

Clinical symptoms are characterized by age dependency both in the initial signs and the clinical course.⁽¹⁾ The age of onset is in childhood around 6 years. However, there are patients who have an onset in adulthood⁽⁷⁾ or at ages older than fifty years.⁽¹⁾ Childhood onset cases start with postural dystonia of a lower extremity, mostly with talipes equinovarus,

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but may start with dystonic posture of one upper extremity at a slightly later age. However, some patients show rigorous dystonic movements; action dystonia, besides postural dystonia. The action dystonia occurs later than postural dystonia from at around 8 years old. It appears commonly as action retrocollis and in some with oculogyric crisis. Writer's cramp or torticollis, that is, focal or segmental dystonia, may appear in adulthood. Postural tremor appears later in the upper extremities mostly after the age of 10 years. Adult onset patients start with hand tremor and gait disturbance due to generalized rigidity. Some start with writer's cramp.

Asymmetry is a characteristic feature and is observed in dystonia, rigid hypertonus and tremor, irrespective of age at onset. Dystonia and tremor show marked diurnal fluctuation, that is, they aggravate towards the evening and recover markedly or nearly completely in the morning after sleep. But these fluctuations are minimal or not apparent in adult onset patients. Patients with onset in early childhood show stagnation of body height with the onset of dystonia and have a short stature of around minus 2 standard deviations by the late teens. This is not observed in patients with onset after adolescence.

Locomotion is preserved and psychomental activities are usually not affected, even in the advanced stages. However some patients show symptoms caused by decreased 5HT activities such as autistic features, depressive state or migraine. Patients with compound heterozygotes show hypotonia, failure in locomotion and delay in mental and motor development.⁽⁸⁾ Clinical courses are also characterized by age dependency. Postural dystonia of one lower extremity in childhood expands to all limbs and develops to generalized dystonia by the middle of the teens, and the grade of rigidity aggravates progressively toward the early twenties. However, the progression attenuates from the late teens and after 30 years, the symptoms become stationary. With the attenuation of the progression, the grade of diurnal fluctuation decreases and becomes in the stationary stage. However tremor, with onset in the early teens, expands to all limbs and the trunk with age and this progression is observed until 30 years.

The presence of action dystonia depends on the family. Thus, clinically, Segawa disease is classified into two types, the postural dystonia type, and the

action dystonia type, with association of vigorous dystonic movements.⁽¹⁾ Patients with action dystonia type may show focal or segmental dystonia in adulthood. Adult onset patients are usually observed in families with action dystonia. Phenotypical variation, which was reported after discovery of the causative gene,⁽⁸⁻¹¹⁾ depends on symptoms observed in patients with action dystonia.⁽¹⁾ There are families with anticipation in the ages at onset and phenotypes, while others show identical features or marked variation in ages at onset or phenotypes irrelevant of the generation.⁽¹⁾

Neurological examination

Muscle stretch reflexes demonstrate rigid hypertonus in Segawa disease. But it is not a plastic rigidity, and repeating the test produces fluctuation in the tonus. The tremor is a high frequency postural tremor (8-10 Hz), but a parkinsonian, resting tremor is not observed. Adult onset patients may show resting tremors of lower frequency. However, the tremor of Segawa disease disappears with a stretch reflex, that is, it does not appear as cogwheel rigidity.

These clinical signs show asymmetry, but the pattern of side predominance of the sternocleidomastoideus (SCM) against that of extremity muscles differs between rigidity and tremor. That is, it is contralateral to that of the extremities for rigidity, but ipsilateral for tremor. However, in adult onset cases the side of predominance of the rigid hypertonus is ipsilateral between the SCM and the muscles of the extremities.⁽¹²⁾ Bradykinesia or postural instability appears with advancing stages of dystonia. However, as locomotion is preserved, a freezing phenomenon is not observed. The tendon reflexes are brisk and ankle clonus may be observed. However the plantar reflexes are flexor, although some patient exhibit a "striatal toe sign"; a sign associated with dysfunction of the basal ganglia. There are neither cerebellar signs nor sensory disturbances. Psychomental activities are preserved normally.

Investigations

Biochemical studies

Cerebrospinal fluid (CSF) examination reveals low levels of homovanillic acid.⁽¹³⁻¹⁷⁾ But characteristic, and pathognomonic features are marked decrease (20-29% of normal levels) of both bipterin and neopterin.⁽¹⁷⁻²⁰⁾ A moderate reduction of these pteri-

dine metabolites is also observed (about 30-50% of normal levels) in asymptomatic carriers.⁽²¹⁾

The activity of GCH 1 in the mononuclear blood cells of patients is less than 20% of that in healthy individuals, while asymptomatic carriers reach 30 to 40% of normal levels.⁽²²⁾ Phenylalanine loading tests in both child and adult patients reveal a six-hour increase in phenylalanine levels.⁽²³⁾ In addition, the phenylalanine to tyrosine ratios remain elevated during the post-loading period, while biopterin levels decline.⁽²²⁾ However, these tracts tend to show false negative results.

Neuroimaging studies

Magnetic resonance imaging and computed tomography scans of the brain show no abnormalities. Positron emission tomography (PET) scanning also demonstrates normal or low normal uptake levels in both [18F] dopa⁽²⁴⁻²⁶⁾ and [11C] raclopride PET^(26,27) in symptomatic subjects. [11C] N-spiperone PET revealed a mild increase in receptor binding,⁽²⁸⁾ but there was no increase in receptor binding in follow-up PET analysis after seven months of levodopa therapy.⁽²⁹⁾ (1R)-2-Carb β omethoxy-3 β -(4-[123I] iodophenyl) tropane ([123I] β -CIT) single photon emission computed tomography (SPECT) scanning was normal.⁽³⁰⁾

Neurophysiological studies

Polysomnography (PSG) reveals abnormalities restricted in the phasic motor components of sleep^(3,31,32) while sleep structure, percent sleep stage and other parameters modulated by the brainstem aminergic neurons and the cholinergic neurons are preserved normally.⁽³⁾ These changes include a decrease in the number of gross movements (GMs), and twitch movements (TMs); and abnormality in the pattern of occurrence of GMs against sleep stages. These phasic components of sleep are modulated by the basal ganglia and the nigrostriatal (NS)-dopamine (DA) neurons. The numbers of TMs during rapid eye movement (REM) sleep reflect the activities of the NS-DA neurons.^(31,32) Normally, the number of REM-associated TMs decreases with age and shows incremental nocturnal variation with the sleep cycle.⁽³¹⁾ In AD GCH 1 deficiency the age-related nocturnal variations of the TMs are preserved, but the number of TMs decreases to approximately 20% or less of normal values.⁽³¹⁾

Abnormalities in the patterns of GMs differ between the postural dystonia and action dystonia types, and that of the latter suggests DA-D₂ receptor supersensitivity.⁽³²⁾ Evaluation of saccadic eye movements reveals abnormalities in both visually guided saccades (VGS) and memory guided saccades (MGS), and implicates involvement of both the direct and indirect pathways.^(33,34) Besides exaggeration of the nigro-collicular inhibition associated with slowing in both saccades, disinhibition of the superior colliculi is postulated by failure in suppression of unnecessary saccade in MGS tasks. This suggests hypofunction of the striatal indirect pathway which disfacilitates the output of the basal ganglia. These abnormalities of MGS are more marked in the action dystonia type than the postural dystonia type. However, in adult onset patients only MGS are affected with preservation of the VGS (Segawa unpublished data).

Supracranial magnetic stimulation was normal, showing preservation of the corticospinal tract.⁽³⁵⁾ Paired pulse transcranial magnetic stimulation showed normal short-interval intra-cortical inhibition of the motor cortex in postural type AD GCH 1 deficiency.⁽³⁶⁾ This suggests that reduction of GABAergic inhibition of the thalamo-cortical pathway may not contribute to generation of dystonia in postural type AD GCH 1 deficiency.

Brain pathology and histochemistry

An autopsy case reported by Rajput et al⁽³⁷⁾ was later revealed to be AD GCH 1 deficiency by gene analysis of the brain.⁽³⁸⁾ Neuropathological examination revealed no demonstrable changes in the substantia nigra (SN) except for a decrease in melanin pigment, particularly in the ventral tier of the pars compacta.⁽³⁷⁾ Histochemically, DA content is reduced markedly in the striatum but mildly in the pars compacta in the SN.⁽³⁹⁾ Similar to Parkinson's disease (PD), the reduction is greater in the putamen than in the caudate nucleus, and subregionally, more in the rostral caudate and the caudal putamen.⁽³⁹⁾ In contrast to PD, AD GCH 1 deficiency shows a greater DA loss in the ventral subdivision of the rostral caudate than its dorsal counterpart, and the activity and protein content of TH are decreased only in the striatum, while they are within the normal range in the SN.⁽³⁹⁾ There are marked reductions of total biopterin (84%) and neopterin (62%) in the putamen, despite normal

concentrations of aromatic acid-decarboxylase, DA transporter and vesicular monoamine transporter.⁽⁴⁰⁾ A post-mortem study on an asymptomatic carrier showed modest reductions of TH protein (52%) and DA (44%), despite marked reduction of striatal biopterin (by 82%).⁽⁴¹⁾

Molecular biological studies

The causative gene of AD GCH 1 deficiency is the GCH 1 gene located on 14q22.1-q22.2.⁽²²⁾ Although more than one hundred independent mutations have now been identified in the coding region of GCH 1, the locus of mutation differs among families but are identical in one family.^(12,22,42) The rate of mutant GCH 1 mRNA production against normal RNA was 28% in one patient but was 8.3% in an asymptomatic carrier.^(43,44) Molecular analysis has been unable to determine mutations in the coding region of the gene in approximately 40% of subjects with AD GCH 1 deficiency.⁽⁴⁵⁾ In some of these subjects, abnormalities in intron genomic deletion,^(42,46) a large gene deletion,⁽⁴⁷⁾ an intragenic duplication or inversion of GCH 1, and mutation in an as yet undefined regulatory gene modifying enzyme function are suspected.⁽⁴⁵⁾

Treatment and prognosis

In most cases, a dose of 20 mg/kg per day of plain levodopa without a decarboxylase inhibitor alleviates the symptoms completely.^(11,48) Some patients starting treatment with plain levodopa before the age of 10 years tend to have a decreased response after around 13 years.⁽⁴⁹⁾ This is due to an increase in decarboxylation in the intestine from around these ages.⁽⁴⁹⁾ To these patients levodopa with a decarboxylase inhibitor alleviates the symptoms completely with doses of 4 to 5 mg/kg/day. In a few patients, choreic movements develop with a rapid increase in dosage or with administration of a higher dose of levodopa in the initial stage of treatment.⁽¹¹⁾ In patients with action dystonia, action retrocollis and oculogyric crisis may be aggregated by initial doses.⁽³²⁾ In patients with the compound heterozygote, aggravation of dystonia with the initial dosage is prominent.⁽⁸⁾ In these patients the unfavorable symptoms disappear with a decrease of the dose. After titration to an optimal dosage by starting with a smaller dose and slowly increasing it, levodopa shows sustained and favorable effects without side

effects.^(8,11) Levodopa is effective without any relation to age of onset and length of the clinical course, and improves short stature if administered before puberty.⁽⁴⁹⁾ However, in cases of action dystonia and adult onset cases, levodopa does not always show complete effects.

Anticholinergic drugs may have a marked and prolonged effect, but do not afford complete relief, either clinically or polysomnographically.⁽⁵⁰⁾ It does not improve the tremor.^(32,50) Amantadine has proven beneficial for levodopa-related chorea.⁽⁵¹⁾ Tetrahydrobiopterin (BH₄) monotherapy is not favorable^(18,52-55) but there are a few patients who show complete remission after administration of BH₄ in addition to levodopa.⁽⁵²⁾ In one patient with the compound heterozygote, administration of BH₄ was necessary for complete recovery.⁽⁸⁾

Pathophysiological considerations

Why patients with heterozygous gene abnormalities develop symptoms

In the pathogenetic mechanisms of dominant inheritance, a classic dominant negative effect^(56,57) and destabilizing effect⁽⁵⁸⁾ have been considered. The ratio of mutant/wild-type GCH 1 mRNA in lymphocytes is higher in an affected individual than an unaffected heterozygote, and varies depending on the locus of the mutation.^(44,58,59) Furthermore, the ratio differs among affected individuals in some families, depending on the locus of the mutation.^(43,58) Thus the degree and the pattern of inactivation of the normal enzyme by the mutant gene differ among the loci of the mutation and may cause inter- and intra-familial variation in the phenotype as well as the rate of penetrance.

Why TH is rather selectively affected

In AD GCH 1 deficiency, TH appears to be preferentially affected when compared to tryptophan hydroxylase. This could be explained by the difference in distribution of GCH 1 mRNA in DA and 5HT neurons,⁽⁶⁰⁾ the destabilization of the molecule of TH or impairment of axonal transport.⁽⁴¹⁾ However, a difference in the Km value for TH and tryptophan hydroxylase⁽⁶¹⁾ is most probable. With the heterozygotic mutant gene, BH₄ decreases partially in AD GCH 1 deficiency. Thus TH with a higher affinity to BH₄ is affected rather selectively. In molecular conditions with marked decreases of BH₄, as in

the compound heterozygote, both tryptophan hydroxylase and TH are affected, producing symptoms induced by deficiencies of the 5HT neurons. Or that is, TH has higher affinity to BH₄. In Segawa disease with heterozygous mutant gene, the BH₄ level is partially decreased, so TH may be affected selectively.

How histochemistry findings relate to clinical symptoms

A complete and sustained response to levodopa suggests a functional lesion restricted to the NS-DA neurons in AD GCH 1 deficiency.^(1,48,62) PET studies show that main lesion is decrease of TH activities in the striatum or the terminal of the NS-DA neuron and that, DA-D₂ receptors and DA transporters are not involved in the pathophysiologies of this disease. These are confirmed by neuropathological and histochemical studies.^(37,39) Histochemical studies further showed the main lesion with decreases of TH or DA in the ventral area of the caudate nucleus.⁽³⁹⁾ In the rostral caudate in particular, the medial/ventral portions, the striosomes/patches or D₁ direct pathways are more numerous, whereas in the dorsal/lateral portions, the matrix compartment is more homogenous.^(63,64) Thus histochemical findings suggest that the DA loss in AD GCH 1 deficiency is more prominent in the striosomes/patches compartment, the terminal for the D₁ receptor.⁽³⁹⁾ TH activity of the NS-DA neurons shows age-related decrement and circadian oscillation in the terminals,⁽⁶⁵⁾ but these age and state-dependent variations are not observed in the pars compacta of the SN.⁽⁶⁶⁾ The age-related clinical course and diurnal fluctuation correlate to the age and circadian variation of the activities of TH in the synaptic terminals of the NS-DA neurons in the caudate.⁽⁶⁵⁾ PSG suggested that the TH activities at the terminal follow the decremental age and incremental nocturnal variation of normal individuals with low levels but without progressive decrement of the activities. These features and the results of PET scan confirm that AD GCH 1 deficiency is not a progressive or degenerative disorder and the NS-DA neurons preserve their fundamental functions. These implicate childhood onset, age-related clinical course and diurnal fluctuation.

How particular symptoms of GCH 1 deficiency develop in childhood

Study of GCH 1 activities in stimulated

mononuclear blood cells shows age-dependent decrement of the activities in the first three decades of life.⁽⁶⁷⁾ Putaminal biopterin levels increase in the postnatal period, reaching a plateau at 1 to 13 years of age, before declining in adulthood.⁽⁶⁸⁾ These results imply that pteridine metabolism has a critical period beginning early in infancy and extending to early childhood. This shows the important roles of GCH 1 and BH₄ for neuronal development in the first and the second decades of life.⁽⁶⁹⁾ Several processes have been considered in the loss of striatal TH protein with normal preservation in the SN. BH₄ may control protein stability rather than expression.⁽⁴⁰⁾ Animal experiments revealed stabilization of TH protein by co-expression of GCH 1⁽⁷⁰⁾ and loss of TH protein but not of TH mRNA in the brains of BH₄ deficient mice.⁽⁷¹⁾ Clinically it is suggested that the D₁ direct pathways mature earlier than the D₂ indirect pathways.⁽⁷²⁾ Dopa-responsive growth arrest seen in children with AD GCH 1 deficiency is a reflection of tuberoinfundibular D₄ receptor involvement. The D₄ receptor belongs to the D₂ receptor family, which, however, matures early among D₂ families.⁽⁷³⁾ Thus, the DA neuron modulated by pteridine metabolism might regulate DA receptors that mature early in the developmental course.

Phenotypical variation is caused by involvement of different DA neurons and serotonergic neurons

Tremor is levodopa responsive but develops independently from symptoms of postural dystonia. A difference in the side predominance of tremor in the SCM and extremities from that in dystonic hypertonus suggests a different pathophysiology of tremor from that of postural dystonia and implies that the responsible lesion is downstream of the striatum for tremor. As tremor is dopa responsive, involvement of the DA neurons innervating to the subthalamic nucleus (STN) with D₁ receptors^(74,75) is postulated. PET findings revealing preservation of function of D₂ receptors⁽³⁶⁾ support this hypothesis, and suggest that the striatal indirect pathway does not play a role in the generation of symptoms.

This also confirms the unresponsiveness of tremor to anticholinergics. In addition, the response of the tremor to stereotactic thalamotomy targeting the ventrolateral (VL) thalamic nucleus, which was performed in the era before levodopa,⁽⁷⁶⁾ suggests involvement of the ascending pathway to the VL

nucleus of the thalamus. Given that the ascending pathways to the thalamus develop later than the descending pathways, increasing age may be a factor for development of tremor.^(1,77)

The side of torticollis and the predominant side of SCM in adult onset cases in families with action dystonia are ipsilateral to the predominant side of rigidity. These implicate the involvement of the DA neurons innervating to the STN in these phenotypes. Involvement of the DA neurons innervating to the STN could explain the ipsilateral involvement of the hypertones between STM and extremity nucleus and also PSG findings suggesting D₂ receptor-upward regulation observed in patients with action dystonia.⁽³²⁾ This also postulates the incomplete response to levodopa observed in some cases of action dystonia and adult onset cases because activation of the D₂ receptors of the striatal indirect pathway by levodopa causes suppression of the STN.

The hypotonia and failure in locomotion observed in patients with compound heterozygotes⁽¹¹⁾ are considered to be a deficiency of 5HT regulated activities.⁽¹⁰⁾ Preservation of interlimb coordination or locomotion in AD GCH 1 deficiency without symptoms of 5HT deficiency may depend on preservation of the descending output of the basal ganglia to the pedunculopontine nucleus.^(1,77,78)

Gender differences are still under consideration

Segawa disease has a gender preference for females.⁽¹⁾ In our series with 28 gene-proved patients from 15 families, the ratio was 25:3.⁽¹⁾ Two studies estimating the ratio of symptomatic carriers revealed identical results with penetrance of gene mutations of 87% and 87% for females and 38% and 35% for males, respectively.^(1,79) A gender difference in the base levels of GCH 1 in the mononuclear blood cells suggested by Ichinose et al⁽²²⁾ is yet to be confirmed. Thus, the marked female predominance might depend on a genetically determined gender difference in the DA neurons.⁽⁸⁰⁾

Postulates for the pathophysiology of AD GCH 1 deficiency

Partial decrement of BH₄ caused by partial GCH 1 deficiency induces decrement of TH protein in the ventral area of the striatum, resulting in development of particular symptoms through the DA D₁ receptors and the neuronal tracts of the basal ganglia which

mature early along with the developmental variation of the enzyme. In childhood, it causes disfacilitation of the D₁ striatal direct pathway, and disinhibits the descending output projection of the internal segment of the globus pallidus and pars reticulata of the SN, which suppress the reticulospinal tract and the superior colliculus. These may cause postural dystonia with exaggeration of the tendon reflexes without extensor plantar reflexes and abnormalities in voluntary saccades. However, with involvement of the DA neuron innervating to the STN with the D₁ receptor, the ascending outputs to the thalamus are disfacilitated and develop tremor and action dystonia later, depending on the functional maturation of the ascending output. As the STN develops early functionally, it causes abnormalities on PSG which mimic D₂ receptor supersensitivity in childhood cases with action dystonia. Because in the state with D₂ receptor supersensitivity the STN is suppressed by disinhibition of the external segment of the globus pallidus. This situation is the same as disfacilitation of the STN by decreased DA activities innervating to this nucleus. Furthermore, this process also disinhibits the superior colliculus and involves failure in suppression of unnecessary saccade in memory guided tasks. The focal and segmental dystonia observed in patients with action dystonia are caused by dysfunction of the motor cortex due to disinhibition of the thalamo-cortical pathway. Considering the ipsilateral involvement of the predominant side of rigidity in the SCM and extremities, this pathway is postulated to involve in adult onset patients. Preservation of VGS in adult onset cases suggest that the direct pathway and the descending output, which mature at early ages, are not involved in the pathophysiology in these patients. This also relates to absence of postural dystonia in adult onset patients. The pathophysiology of the postural and action dystonia types are shown in Figs 1A and 1B.

Diagnosis

Diagnosis of AD GCH 1 deficiency is usually not difficult in the setting of characteristic clinical symptoms. As gene studies show false negative results, estimation of GCH 1 activity in peripheral mononuclear cells gives a definite diagnosis, but this is technically complicated. Thus, estimation of neopterin and biopterin levels in the CSF is most reliable for diagnosis.

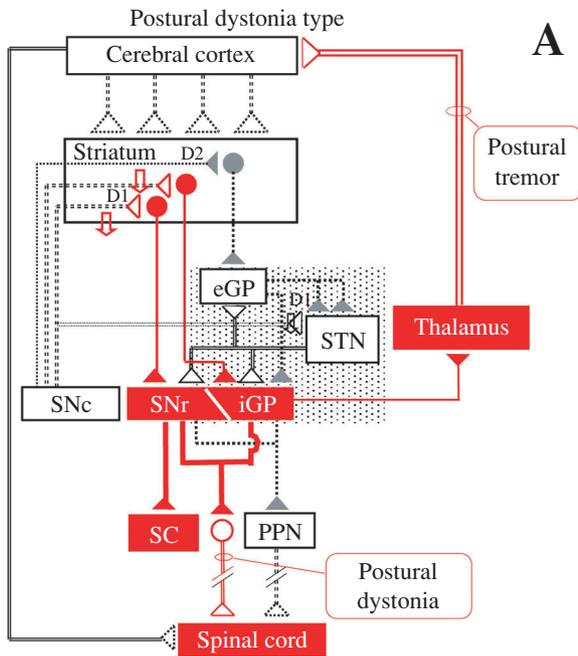


Fig. 1A Postural dystonia type. Abbreviations: eGP: external segment of the globus pallidus; iGP: internal segment of the globus pallidus; STN: subthalamic nucleus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; SC: superior colliculus; PPN: pedunculopontine nucleus. The red background shows the structures involved; Symbols: Red solid, single and open lines and triangles: pathways and terminals involved in pathophysiology; The width shows degree of activities; Dotted lines: pathways not involved in pathophysiology; Single line: inhibitory neuron; Open line: excitatory neuron; Closed triangle: inhibitory neuron; Open triangle: excitatory neuron; Shaded region with dots: the area of the circuit for postural tremor.

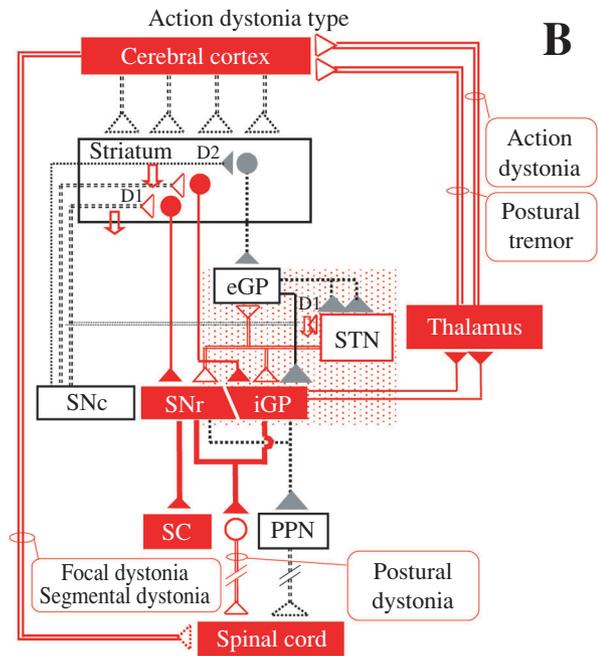


Fig. 1B Action dystonia type. Abbreviations: eGP: external segment of the globus pallidus; iGP: internal segment of the globus pallidus; STN: subthalamic nucleus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulata; SC: superior colliculus; PPN: pedunculopontine nucleus. The red background shows the structures involved. Symbols: Red solid, single and open lines and triangles: pathways and terminals involved in pathophysiology; The width shows degree of activities; Dotted lines: pathways not involved in pathophysiology; Single line: inhibitory neuron; Open line: excitatory neuron; Closed triangle: inhibitory neuron; Open triangle: excitatory neuron; Shaded region with dots: the area of the circuit for postural tremor.

Differential diagnosis

All children with gait disturbance and limb dystonia with asymmetry should be evaluated for AD GCH 1 deficiency. The differential diagnosis includes Wilson's disease, pantothenate kinase-associated neurodegeneration (Hallervorden-Spatz disease), hereditary spastic paraplegia and cerebral palsy. AD GCH 1 deficiency is often misdiagnosed as hereditary spastic paraplegia. The differentiation of AD GCH 1 deficiency from these disorders is usually not difficult with careful clinical examination.

Cases of axial torsion dystonia in childhood, including early onset autosomal dominant torsion dystonia (DYT1), can be differentiated clinically

from AD GCH 1 deficiency by evaluating the side predominantly involved between the SCM and muscles of the extremities; that is, it is contralateral in AD GCH 1 deficiency, while it is ipsilateral in dystonias with axial torsion. DYT1 also has two clinical types, postural dystonia and action dystonia.⁽⁸¹⁾ The involved neuronal pathways of the basal ganglia for postural dystonia are the same in both diseases. However, in the action dystonia of DYT1, the striatal indirect pathways are involved with preservation of the STN. This may relate to the presence of motor tricks in DYT1 with action dystonia, while it is not observed in the action dystonia of AD GCH 1 deficiency. However, it should be taken into considera-

tion that adult onset patients in families with the action dystonia type of DYT1, have focal or segmental dystonia, not general dystonia as in adult onset patients in families with the action dystonia type AD GCH 1 deficiency. Differentiation of these patients with a levodopa loading test is recommended, in addition to biochemical and molecular biological studies.

In addition to AD GCH 1 deficiency, dopa-responsive dystonia is also observed in recessive deficiency of pteridine metabolism, recessive TH deficiency (recessive DYT 5) and juvenile parkinsonism (JP).

All of the recessively inherited disorders of pteridine metabolism develop levodopa responsive dystonia caused by a decrease of BH₄ in infancy and early childhood, as in AD GCH 1 deficiency. However, they show levodopa non-responsive postural hypotonia and psychomotor disturbances which are caused by deficiency of 5HT activities. Interestingly, recessive sepiapterin reductase deficiency only shows action dystonia⁽⁸²⁾ suggesting involvement of the DA neurons innervating to the STN. Patients with recessive TH deficiency show ptosis, hyperperspiration and psychomotor disturbances due to noradrenalin (NA) deficiency.⁽⁸³⁾ Some patients show features almost identical to AD GCH 1 deficiency and the disease responds well to levodopa,⁽⁸⁴⁾ however the diurnal fluctuation is not marked as in AD GCH 1 deficiency and patients later develop parkinsonian symptoms due to involvement of D₂ receptors. This is because in recessive TH deficiency, the terminals of DA neurons innervating to the dorsal area of the striatum are involved.⁽⁸⁵⁾ For a definite diagnosis of these disorders, estimation of pteridine metabolites and catecholamine metabolites in the CSF is necessary.

JP appears as dystonia when it occurs in childhood to early teens.⁽⁸⁶⁾ Although the dystonia of JP responds briskly to levodopa, dyskinesia develops soon after levodopa is started, so it is necessary to start with Dopa agonists in these patients. At this point, JP which is caused by the *parkin* gene (PARK2) is a particularly important disease to differentiate from AD GCH 1 deficiency when it occurs at early ages.

Some patients with AD GCH 1 deficiency develop symptoms later in life (e.g. the fifties and sixties), with tremor, rigidity and gait disturbance but

without dystonia. In these patients diurnal fluctuation is not observed and the disease is often misdiagnosed as PD. However, the tremor in these cases is mainly postural and clinical features are milder with minimal progression and without cogwheel rigidity. The most important clinical sign for the differential diagnosis is the side of the predominance of the rigidity between the SCM and the extremities. That is, it is ipsilateral in these patients in contrast to contralateral involvement in JP and PD. Normal preservation of the voluntary saccade in PARK 2 is also diagnostic. However, for definite diagnosis of PARK2, gene analysis is necessary.

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