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# Dystonia and Dopaminergic Therapy: Rationale Derived from Pediatric Neurotransmitter Diseases

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## 1. Introduction

The paucity of literature in pediatric neurotransmitter diseases indicates a gap in our understanding of neurochemistry and the clinical phenomenology. However, the dramatic clinical responses to dopaminergic therapy in dopa-responsive dystonias opened avenues for rationalizing this therapeutic approach in other pediatric neurotransmitter disorders. This chapter aims to link up dopaminergic therapy, dystonia and other pediatric neurotransmitter diseases. It was in 1971 that Segawa (Segawa et al., 1971, 1976) reported patients with child-onset periodic dystonia, whose dystonia had diurnal variation, with towards evening being worse with walking. The symptom was recovered in the morning. Unlike other dystonic disorders, levodopa was effective to alleviate involuntary movements in those patients. (Tarsy et al., 2006) This disease was later named as Dopa responsive dystonia (DRD), DYT-5, or Segawa disease. (Nygaard et al., 1988)

In 1994, Ichinose et al. detected that the cause of Segawa disease was heterozygous defect of guanosine triphosphate cyclohydrolase I (GTPCH) located at 14q22-q22.2. (Ichinose et al., 1994) GTPCH is a rate-limiting enzyme of tetrahydrobiopterin (BH4) synthesis from guanosine triphosphate (GTP). (Shintaku, 2002) BH4 is co-factor of aromatic amino acids hydroxylase. Tyrosine hydroxylase (TH) is one of aromatic amino acids hydroxylase and it is a rate-limiting enzyme of dopamine synthesis. In Segawa disease, decrease of BH4 is considered to suppress the activity of TH and dopamine production. Dopamine begins to be used up after waking up and the individual becomes active. In effect, the total amount of dopamine in terminals of dopaminergic neurons decrease in the evening, when dystonic symptoms occur. At night, during sleep as one rests, dopamine is recharged such that upon waking up, no dystonia is noted (Furukawa et al., 1999, 2002; Segawa et al., 2003).

It was reported that other diseases showed symptoms of dystonia and other movement disorders that were responsive for L-dopa. There were tyrosine hydroxylase deficiency and sepiapterin reductase (SR) deficiency. Defect of several other enzymes that were related BH4 metabolism, that is, 6-pyruvoyl tetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, and autosomal recessive GTPCH deficiency also demonstrate dopa-responsive involuntary movements. However, those disorders have been considered as diseases related phenylketonuria, for those diseases showed hyperphenylalaninemia and it is

important to reduce phenylalanine concentration in central nervous system (CNS) in patients with those diseases. Some patients with familial parkinsonism also indicated dopa-responsive movement disorder that was resemble for Segawa disease. (Tassin et al., 2000) However, those diseases were considered as a parkinsonism and were not considered as PNDs.

## 2. Pediatric neurotransmitter diseases

In addition to Segawa disease, several disorders related to dopamine/serotonin metabolism have been reported. Disorders of gamma amino butyric acid (GABA) metabolism were also rare metabolic diseases. They were all rare inherited metabolic diseases. Those disorders were called as pediatric neurotransmitter diseases (PND) (Swoboda et al., 2002; Pearl et al., 2007), for they showed involuntary movements due to defect or excess of neurotransmitters from childhood. In this report, the author described summary of clinical manifestations and current treatments of those diseases.

### 2.1 Disease of BH4 metabolism

BH4 is constructed from GTP by several enzymes. Defect of these enzymes decrease the amount of BH4. As BH4 work as co-factor of each aromatic amino acids hydroxylase, suppression of BH4 production affect the synthesis of neurotransmitters. As kinetics of each aromatic amino acids hydroxylase was different, degree of suppression of BH4 synthesis is important to decide the manifestation of each patient. Complete defect of BH4 causes hyperphenylalaninemia, for all of each aromatic amino acids hydroxylase. Those diseases are usually classified as disorders related phenylketonuria and are not considered as PNDs. Two disorders, Segawa disease and Sepiapterin reductase (SR) deficiency, are classified as PNDs, for these diseases indicate normal serum phenylalanine concentration.

In this section, the author described about those two diseases.

However no essential difference was existed between the two diseases and other BH4 deficiency. Plasma phenylalanine level of Segawa disease was significantly higher than those of controls. (See Fig.1) However the values of plasma phenylalanine were within the normal range (less than 2 mg/dl or 121 μmol/l). (Fujioka et al., 2009) Activity of phenylalanine hydroxylase was slightly suppressed in Segawa disease patients. In this chapter, diseases of BH4 deficiency with hyperphenylalaninemia are also described simply.

### 2.1.1 Segawa disease

Segawa disease was first reported PNDs and caused by partial defect of GTPCH. (Segawa et al., 1971; Ichinose et al., 1994) This disorder is autosomal dominant inheritance with incomplete penetrance. (Furukawa et al., 1998) Most of patients showed dystonic symptoms before 7 year-old. Adult-onset Segawa disease was also reported. (Turjanski et al., 1993) Number of female patients was reported to 2 to 6 times higher than those of male patients. (Furukawa et al., 1998) The most popular symptom of Segawa disease is postural dystonia. (Segawa et al., 2003) In these patients, often dystonia in one side of legs was observed. The dystonic symptoms were often spread to both sides of upper and lower limbs around 15 year-old. Muscle rigidity progressed around 20 year-old. After that, most of their symptoms were fixed. In a part of these patients, postural tremor was also observed. In other patients, action dystonia was observed. Those patients often showed involuntary movements after 8 year-old.

Their symptoms were often upper-limb dystonia, cervical dystonia, or oculogyric crisis. After the age of young adult, they also showed spasmodic torticollis, or writer's cramp. Some patients with action type Segawa disease showed paroxysmal kinesigenic dyskinesia or restless leg syndrome-like symptoms. Adult-onset type Segawa disease patients showed spasmodic torticollis, or writer's cramp, parkinsonism-like symptoms.
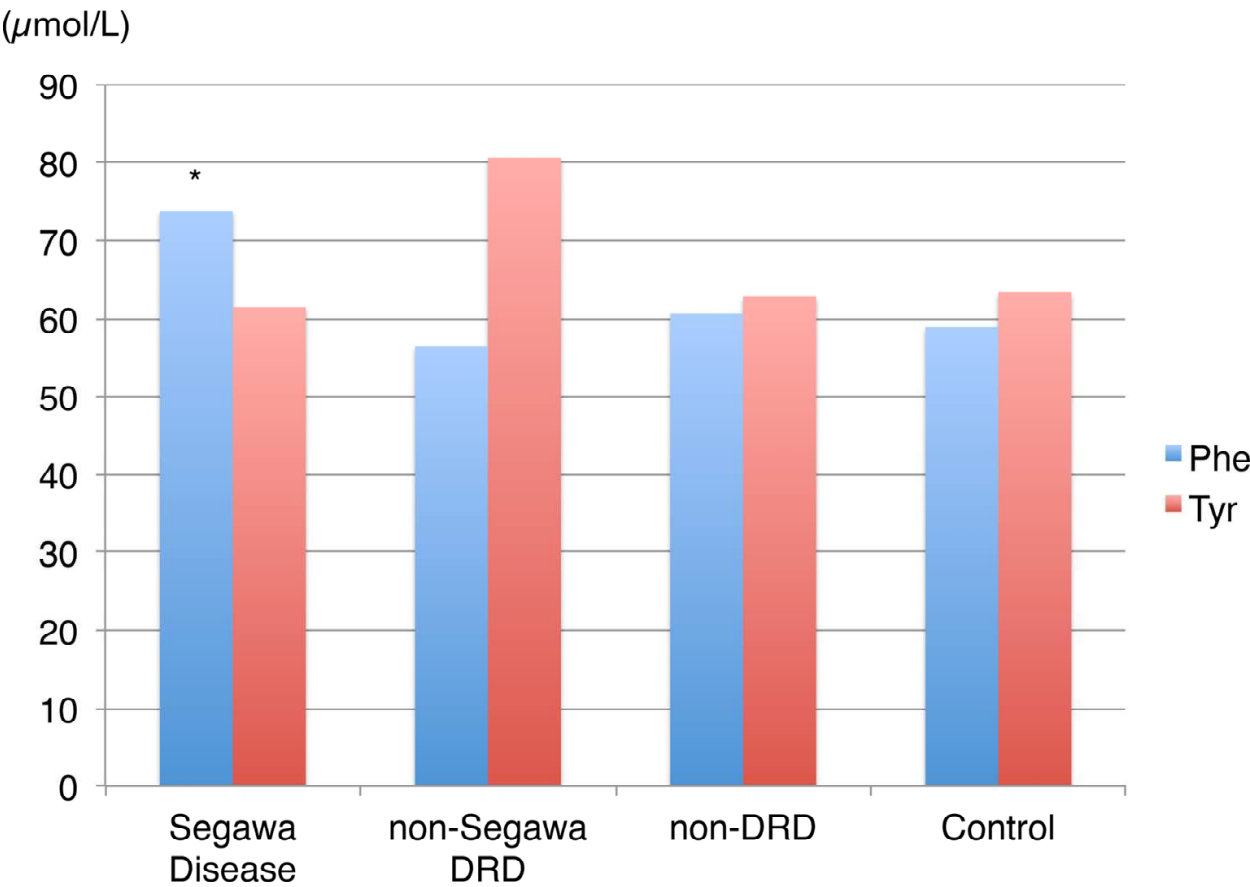
($\mu$mol/L)



Fig. 1. Comparison of plasma phenylalanine (Phe) and Tyrosine (Tyr) concentration. (Modified from Fujioka et al., 2009)

Analysis of variance indicated that plasma phenylalanine concentration of Segawa disease was higher than those of other group (asterisk: $p < 0.05$). However, the value was within the normal range (less than 121μmol/l). No significant difference was observed in plasma tyrosine concentration.

Usually patients of Segawa disease did not show psychomotor delay or convulsion. Their locomotion was also normal. However some Action type patients showed depression. Several patients who occurred symptoms during infantile periods often showed autistic tendency, depression, obsessive-compulsive disorders, or headache that suggested shortage of serotonin. In those patients, decrease of muscle tonus or abnormality of locomotion was also observed.

To diagnose Segawa disease is difficult, for its symptom is broad. (Chaila et al., 2006) Gene analysis of GTPCH enzyme is one of good method to diagnose Segawa disease, however, mutation of GCH1 gene, which is coding GTPCH, has been reported various. Some reports described that a part of patients with dopa-responsive dystonia and clinically diagnosed as Segawa disease did not have any mutation in GCH1 gene. (Zirn et al., 2008) Biochemical

diagnose of Segawa disease has also been reported. One method is oral phenylalanine loading test. (Hyland et al., 1997; Bandmann et al., 2003; Opladen et al., 2010)  As activity of GTPCH of Segawa disease patients is lower than that of control, amount of neopterin, a metabolite of biopterin synthesis pathway (Fig. 2) in cerebrospinal fluids (CSF) is expected to decrease. (Fujita et al., 1990; Furukawa et al., 1993; Bandmann et al., 1996)  Amount of BH4 in CNS of patient with Segawa disease also decreased. (Furukawa et al., 1999)
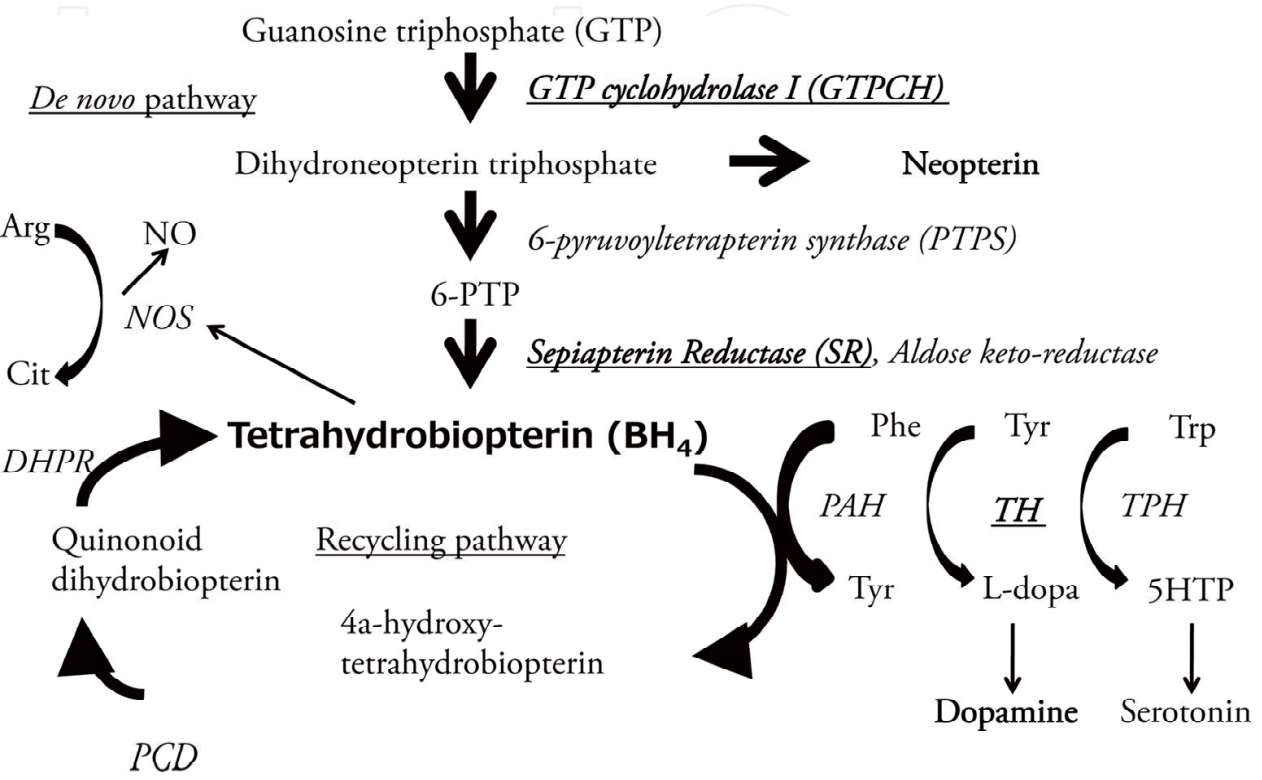


Fig. 2. Scheme of Tetrahydrobiopterin Synthesis and metabolism.

Tetrahydrobiopterin is synthesized from GTP by GTP cyclohydrolase I (GTPCH), Sepiapterin reductase (SR), and other enzymes. BH4 is a co-factor of each aromatic amino acid hydroxylase. Tyrosine hydroxylase (TH) is one of aromatic amino acid hydroxylase, which convert Tyrosine into L-dopa.

As described in original reports, levodopa was effective to many of Segawa disease patients. The maximum dose of levodopa is 20 mg/kg/day. (Segawa et al., 2003; Furusho et al., 1993) Carbidopa is an inhibitor of dopa decarboxylase. To use drugs of the levodopa/carbidopa combination, amount of L-dopa delivering to neurons was increasing, for it prevent to convert L-dopa to dopamine outside the blood-brain barrier. (Nagata et al., 2007; Bernard et al., 2010)  In recent report, low dose levodopa and selegiline was helpful. (Yosunkaya et al., 2010)  However, in some patients of action type Segawa disease, levodopa was not effective, for it was considered that the dysfunction of D1 receptor of dopaminergic neurons in hypothalamus. (Segawa et al., 2003)  In these patients, D1 agonists would be effective. In patients showed shortage of serotonin, 5-hydroxy tryptophan that was the precursor of serotonin would be effective. BH4 is also effective in these patients, for it is known as a co-factor of both tyrosine hydroxylase and tryptophan hydroxylase, which were the rate-limiting enzymes of synthesis of dopamine and serotonin.

As many of Segawa disease are female and their symptoms occur from childhood, a part of them should be pregnant with symptoms and L-dopa replacement therapy. Treatment of Segawa disease during pregnancy has been reported. (Watanabe et al., 2009) A report from Japan, levodopa monotherapy is relatively safe. Six pregnancies with levodopa monotherapy (Levodopa: 250 mg/day) were safe and three pregnancies were fatal loss, two of them were treated with levodopa/carbidopa (100 mg levodopa + 10 mg carbidopa) and the rest one of them was treated without any medication.

### 2.1.2 Sepiapterin reductase (SR) deficiency

Sepiapterin reductase deficiency has been reported by a patient with progressive psychomotor delay with increase of biopterin and dihydrobyopterin and decrease of 5-hydroxy acetic acid (5-HIAA) and homovanilic acid. (Bonafé et al., 2001) Many of patients were reported around Mediterranean. (Neville et al., 2005) Sepiapterin reductase is one of enzymes to covert sepiapterin into BH4. (See Fig.2)

Patients from Malta showed early motor delay and a significant degree of cognitive impairment. Diurnal variation of the motor impairments and oculogyric crisis occurred from an early stage. Hypotonia was apparent in early stage and later, dystonia was observed. Some of them showed Parkinsonian tremor or chorea. Some of them showed bulbar involvements.

L-dopa dramatically improved motor problems including dystonia, chorea, and oculogyric crisis in those patients. After the treatment, many of them were able to walk. There was no obvious response to cognitive function with learning. In SR deficiency, dysfunction of serotonin was also suspected. It is possible that 5-hydroxy tryptophan is also effective with SR deficiency, for 5-HTP is the precursor of serotonin. Initial dose of L-dopa was 1.5 to 4 mg/kg/day (12.5 to 50 mg/day). (Neville et al., 2005) In these patients, 100 mg L-dopa and 10 mg Carbidopa tablets were used. One case report described incomplete response to treatment during short-term follow-up. (Kusmierska et al., 2009)

| Diseases | Segawa Disease | SR deficiency |
|---|---|---|
| Cause of Gene | GTPCH I (Heterozygous) | Sepiapterin Reductase (SR) |
| Inheritance | Autosomal Dominant | Autosomal Recessive |
| Involuntary Movement | Postural Dystonia, Tremor Action Dystonia | Motor Delay, hypotension Oculogyric crisis, writer's cramp |
| Convulsion | Very Rare | Rare |
| Intellectual | Normal | Delay |
| Hyperphenylalaninemia | - | - |
| CSF Neopterin Level | Decrease | Normal |
| CSF Biopterin Level | Decrease | Increase |
| Dopa Responsibility | + | + |
| Diagnosis | Gene analysis, decrease of CSF neopterin | Gene analysis |
| Treatment | L-dopa (or L-dopa with carbidopa)* | L-dopa with carbidopa |

*carbidopa is not recommended with pregnant women.

Table 1. Disorders of BH4 metabolism

### 2.1.3 other tetrahydrobiopterin defects with hyperphenylalaninemia

Tetrahydrobiopterin is a co-factor of aromatic amino acids hydroxylase. There are three aromatic amino acids hydroxylase, which are tyrosine hydroxylase, tryptophan hydroxylase, and phenylalanine hydroxylase. (Fig. 2) Decrease of tetrahydrobiopterin in liver down-regulates the activity of phenylalanine hydroxylase and blood phenylalanine concentration increase. These include autosomal-recessive GTPCH deficiency (Opladen et al., 2011), pterin-carbinolamin dehydratase deficiency, dihydropteridine reductase deficiency, and 6-pyruvoyl tetrahydropterin synthase deficiency. (Shintaku, 2002) All are autosomal recessive inheritance disorders.

Defect of phenylalanine hydroxylase causes phenylketonuria (PKU) and the most common treatment of PKU is restriction of protein. Large neutral amino acid is another treatment, which decrease brain phenylalanine level.

In contrast, oral administration of tetrahydrobiopterin rapidly normalizes hyperphenylalaninemia s with disorders of tetrahydrobiopterin deficiency. Unlike normal PKU, protein restriction is not effective to decrease serum phenylalanine concentration. Treatment of BH4 deficiency is administration of BH4 (10 mg/kg/day). (Shintaku, 2002) Recently, tetrahydrobiopterin responsive PKU was reported and administration of tetrahydrobiopterin is a new treatment of PKU.

Oral supplementation of BH4 improves the activity of liver phenylalanine hydroxylase and normalizes blood phenylalanine concentration. (Shintaku et al., 2004)

However administration of BH4 does not improve movement disorder due to shortage of dopamine and/or serotonin in CNS, for BH4 do not go through blood-brain barrier. To improve their movement disorders due to insufficient dopamine and/or serotonin, administration of precursor of dopamine and/ or serotonin is necessary to go through blood-brain barrier. Clinically, levodopa and 5-HTP are often used to patients with BH4 deficiency. Carbidopa are also used in addition to levodopa.

## 2.2 Disease of monoamine metabolism

Tyrosine hydroxylase deficiency and Aromatic amino acids decarboxylase deficiency are classified as disorders of monoamine synthesis. In these diseases, symptoms are induced by decrease of amounts of monoamines. Monoamines include dopamine, serotonin, noradrenaline, adrenaline, histamine and other catecholamine. Diseases classified as monoamine breakdown includes monoamine oxidase deficiency and dopamine β-hydroxylase deficiency.

### 2.2.1 Tyrosine hydroxylase deficiency

Tyrosine Hydroxylase (See Fig. 2 and 3) converts tyrosine into L-dopa, and is a rate-limiting enzyme of dopamine synthesis. (Castaigne et al., 1971; Rondot et al., 1983, 1992) Most of patients with tyrosine hydroxylase deficiency showed progressive encephalopathy. (DE Lonlay et al., 2000; Hoffmann et al., 2003) Some other patients showed typical dopa-effective dystonia. Unlike to Segawa disease, neopterin and biopterin concentration in CSF are normal. (Lüdecke et al., 1996)

The former severe type shows axial hypotonia, hypokinesia, and facial mimicry within a few months after birth. After that, increase of deep tendon reflexes, pyramidal movement disorder, oculogyric crisis, ptosis, miosis, and prolonged diurnal periods of lethargy with increased sweating alternated with irritability are also observed. The progress of those symptoms would be sometimes lethal. No effective treatment has been reported. Recently trial of deep brain stimulation was reported to improve severe involuntary movements with a TH deficiency patient. (Tormenti et al., 2011)

The latter mild type patients show involuntary movements responsible for levodopa however did not show any psychomotor delay or convulsion. Their dystonic symptoms and rigidity occur during infantile period. Many of these patients show lower limb dystonia and then the dystonic symptoms spread to other lesions. Some patients also show tremor. They are treatable by levodopa as Segawa Disease. (Willemsen et al., 2010)

### 2.2.2 Aromatic amino acid decarboxylase (AADC) deficiency

Aromatic amino acids decarboxylases convert L-dopa into dopamine and 5-HTP into serotonin. (See Fig.3) Patients of AADC deficiency showed intermittent oculogyric crisis and dystonia of four limbs before 6 month-old. (Korenke et al., 1997; Swoboda et al., 1999, 2003) Irritability, ocular convergence spasm, facial dystonia, myoclonus, and dysfunction of voluntary movements were often observed. Hypotonia and increase of deep tendon reflex were observed. Many of patients were lawn down and were not able to speak. However, the symptoms of AADC deficiency were various, for a mild type patient showed only a mild hypotonia and ptosis. The patient could walk and talk. Some of the patients would be misdiagnosed as cerebral palsy. FDG-PET findings indicated decrease of sugar metabolism at striatum. (Sato et al., 2006; Ide et al., 2010) Dysfunction of basal ganglia should be a cause of abnormal movements.
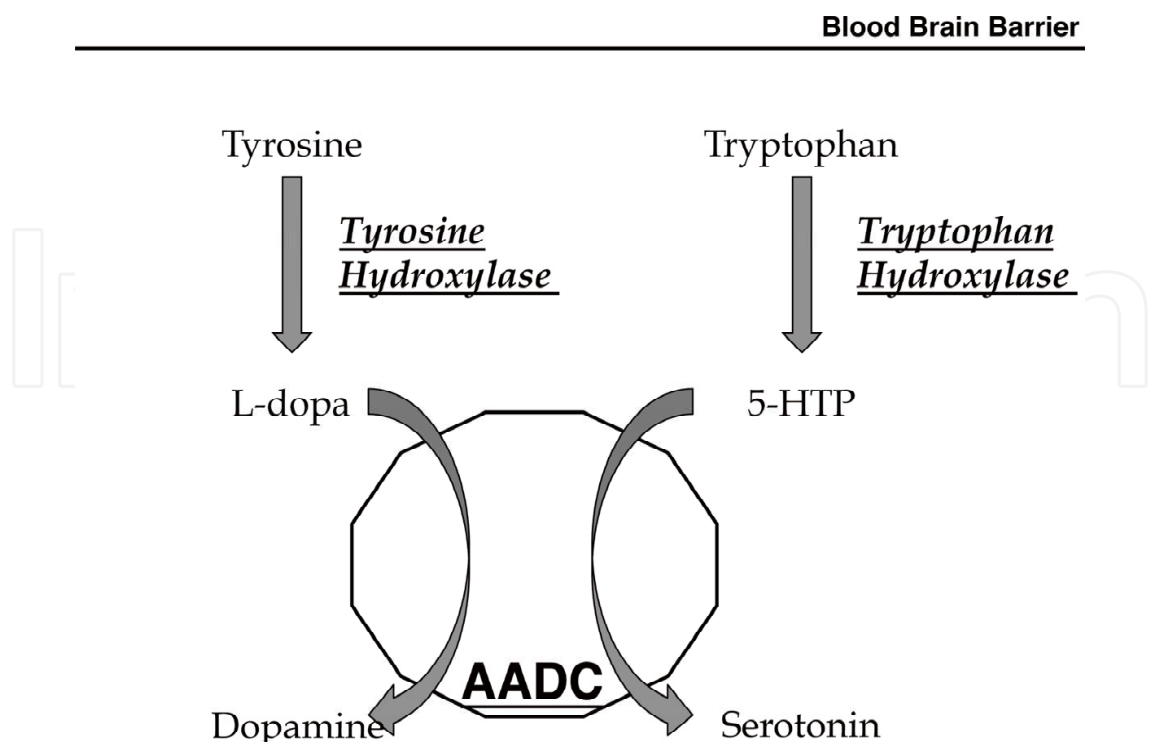


Fig. 3. Structure and Function of Aromatic l-amino acid decarboxylase (AADC).

Due to shortage of catecholamine, sweating, breath holding, diarrhea, and ptosis were observed in most patients with AADC deficiency. In some patients, convulsion due to hypoglycemia was reported. (Korenke et al., 1997; Swoboda et al., 1999, 2003) Sleep disorder was also observed in a part of patients, for amount of melatonin is decreased in patients with AADC deficiency. Melatonin is synthesized from serotonin and amount of serotonin often decrease in patients with AADC deficiency. Some patients have epilepsy or abnormal electroencephalogram. (Pearl et al., 2007; Bräutigam et al., 2002; Ito et al., 2008)

Tyrosine and Tryptophan are converted into L-dopa and 5-HTP by their aromatic acids hydroxylase. The produced L-dopa and 5-HTP are converted into dopamine and serotonin by aromatic l-amino acids decarboxylase (AADC). Increase of L-dopa and decrease of dopamine is observed in CNS when AADC do not work in patients with AADC deficiency, for dopamine is not allowed to go through blood brain barrier

Dopamine agonists, monoamine oxidase inhibitors, and vitamin B6 are used as a medication for AADC deficiency. Vitamin B6 is a co-factor of AADC. (Pons et al., 2004; Brun et al., 2010) However these drugs has not been improved the symptoms of AADC deficiency patients well. Now, gene therapy is expected as a novel therapy for those patients. As the construct of brain in AADC deficiency patients are normal, their symptoms is expected to be improved when AADC enzyme work well in their brain. (Manegold et al., 2009; Allen et al., 2009; Jarraya et al., 2009)

| Diseases | TH deficiency | AADC deficiency |
|---|---|---|
| Cause of Gene | Tyrosine Hydroxylase | Aromatic L-amino acid Decarboxylase |
| Inheritance | Autosomal Recessive | Autosomal Recessive |
| Involuntary Movement | DRD, | Oculogyric crisis, |
| | Progressive encephalitis | Postural Dystonia of extremities |
| Convulsion | Rare | Not common |
| Intellectual | DRD type: normal, | Delay |
| | encephalitis type: delay | |
| Diagnosis | Gene analysis, decrease | Gene analysis, increase of |
| | of Homovanilic acid (HVA) | L-dopa and 5-HTP |
| Dopa Responsibility | + | - |
| Treatment | L-dopa (DRD), | Dopamine agonist, MAO inhibitor, |
| | None (encephalitis) | Vit. B6, Gene therapy |

Table 2. Disorders of Dopamine metabolism

### 2.2.3 Monoamine oxidase deficiency

Monoamine oxidase (MAO) has two isotypes, MAO A and MAO B. Both genes are on the X chromosome. Mutation of MAO A gene was reported in a large family. (Brunner et al., 1993)

All affected males showed mild mental retardation and aggressive behaviour. No MAO B deficiency has been reported.

### 2.2.4 Dopamine β-hydroxylase deficiency

Dopamine β-hydroxylase is a copper-dependent enzyme and it converts dopamine into noradrenalin. Dopamine β-hydroxylase deficiency (Robertson et al., 1986) is rare autosomal recessive disorder and showed orthostatic hypotension due to deficit in autonomic regulation. Other symptoms of this disease are impaired ejaculation, ptosis, nocturia, hyper flexible joint, high palate, nasal stiffness, and so on. (Robertson et al. 1991) To treat orthostatic hypotension, L-threo-3, 4-dihydroxyphenylserine (DOPS) were reported. (Biagginoni et al., 1986; Freeman et al., 1991)

### 2.3 Disorders of GABA metabolism

Gamma amino butyric acid is important inhibitory neurotransmitters. Failure of GABA regulation induces various neurologic symptoms. Glutamic acid decarboxylase (GAD) deficiency is disorder of GABA synthesis. GABA transaminase deficiency and succinic semialdehyde dehydrogenase (SSADH) deficiency are disorders of GABA breakdown.

### 2.3.1 Glutamic acid decarboxylase (GAD) deficiency

Glutamic acid decarboxylase (GAD) synthesizes GABA from glutamate. GAD1 deficiency is autosomal recessive inheritance and it was reported that the disease was a cause of non-progressive form of spastic cerebral palsy. (Lynex et al., 2004) Other report described that animal model of GAD deficiency was related to cleft palate. (Asada et al., 1997) Suppression of GAD by autoantibody was reported to relate Batten disease (Pearce et al., 2001) or epilepsy. (McKnight et al., 2005)

### 2.3.2 GABA transaminase deficiency

GABA transaminase (See Fig.4) converts GABA into succinate. Deficiency of GABA transaminase is autosomal recessive inheritance. Only three reports have been published about patients with GABA transaminase deficiency. They showed severe psychomotor retardation, hypotonia, hyperreflexia, lethargy, and refractory seizures. (Jaeken et al., 1984; Medina-Kauwe et al., 1999; Tsuji et al., 2010) The patients showed growth acceleration due to elevation of serum growth hormone concentration. Increase of GABA in blood and CSF is important to diagnose GABA transaminase deficiency. The recent study described that increase of intracranial GABA was detected by proton magnetic resonance spectroscopy ($^1$H-MRS). (Tsuji et al., 2010) This report also described that the prenatal exposure of GABA was responsible for the clinical manifestation of this disease, for GABA worked as an excitatory molecule early in life.

### 2.3.4 Succinic semialdehyde dehydrogenase (SSADH) deficiency

Succinic semialdehyde dehydrogenase (SSADH) converts succinic semialdehyde into succinate. (See Fig.4) In SSADH deficiency patients, dysfunction of SSADH causes increase

of 4-hydroxybutylic acids. (Gibson et al., 1983; Rating et al., 1984)  However, it is not confirmed that 4-hydroxybutylic acids is the cause of symptoms, for the substance negate the symptoms of SSADH deficiency when it was administrated for patients or model animals. SSADH deficiency is one of disorders of gamma amino butyric acid (GABA) metabolism.

Symptoms of SSADH deficiency are mild to moderate developmental delay, severe hypotonia, sleep disorder, attention deficit, hyperactivity, anxiety, decrease of deep tendon reflex, non-progressive cerebellar ataxia, and convulsions. Most of SSADH patients are non-progressive. However, 10% of SSADH patients are progressive. Cranial T2 weighted MRI indicated high signal in both side of globus pallidus. (Pearl et al. 2011, Yamakawa et al. 2011)

No effective treatment is known. In a part of patients, vigabatrin (gamma vinyl GABA) is reported to improve symptoms of ataxia. Vigabatrin is an inhibitor of GABA transaminase. (Gibson et al., 1989, 1995; Gropman et al., 2003)
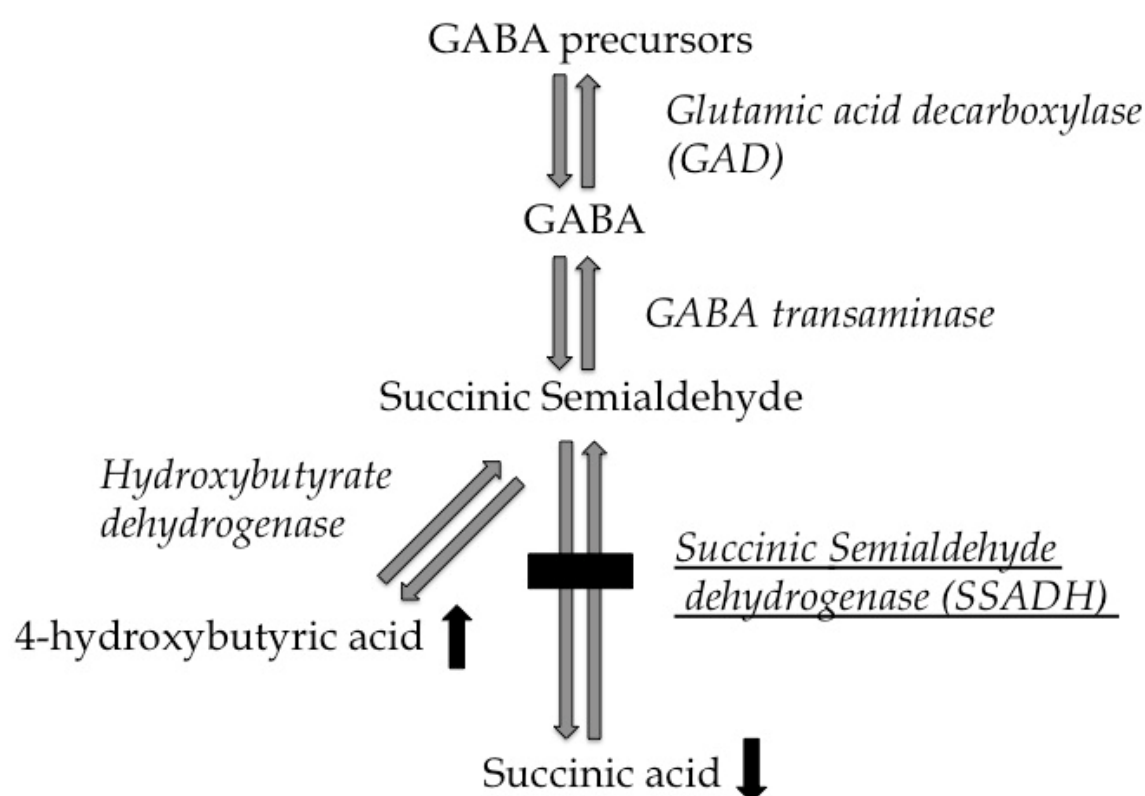


Fig. 4. Metabolism of GABA and SSADH deficiency

GABA is converted into succinic semialdehyde by GABA transaminase. Succinic semialdehyde is catalysed to 4-hydroxybutyric acid and succinic acid. In patients with succinic semialdehyde dehydrogenase (SSADH) deficiency, Succinic acid decrease and 4-hydroxybutyric acid increase.

| Diseases | GAD deficiency | GABA transaminase deficiency | SSADH deficiency |
| --- | --- | --- | --- |
| Inheritance | Autosomal Recessive | Autosomal Recessive | Autosomal Recessive |
| Involuntary | Spastic cerebral palsy | Psychomotor delay, hypotonia | Motor delay, hypotonia, |
| Movement | Cleft palate? | hyperreflexia, lethargy, seizure | convulsion, sleep disorder, |
| Convulsion | relation to epilepsy? | common | common |
| Intellectual | Delay | Delay | Delay |
| Diagnosis | Gene Analysis | Increase of blood and CSF GABA | Gene analysis, increase of |
| | | proton MRS | urine gamma-hydroxy butyrate |
| Treatment | None | None | Vigabatrin |

Table 3. Disorders of GABA metabolism

## 3. Conclusion

Pediatric neurotransmitter diseases were induced by congenital defects of neurotransmitters. Diseases related to dopamine/serotonin system affected basal ganglia and patients showed dystonia and other involuntary movements. L-dopa was effective to those disorders, for those symptoms were induced by shortage of dopamine in central nervous system. L-dopa is a precursor of dopamine and is able to go through blood-brain barrier. So oral administrated L-dopa is converted into dopamine in brain. Administration of dopamine is no effect because it does not go through blood-brain barrier. In patients with AADC deficiency, L-dopa is not effective. In those patients, dopamine is not synthesized from L-dopa in CNS, for AADC is inactive. (See Fig. 3)

Some of patients of PNDs show decrease of serotonin. Psychiatric symptoms including depression, sleep disorder, obsessive-compulsive disorders, or headache is often observed when serotonin deficiency occurs. In those patients, 5-HTP is useful to supply serotonin, for 5-HTP is a precursor of serotonin and is able to go through blood-brain barrier.

Tetrahydrobiopterin (BH4) is co-factors of dopamine and serotonin synthesis. (Fig. 2) Administration of BH4 is useful to reduce hyperphenylalaninemia in liver. The administration of BH4 could increase the production of innate L-dopa or 5-HTP at outside of CNS, for BH4 do not go thorough blood brain barrier. However, BH4 is insufficient to improve intracranial abnormality of dopamine and serotonin. Administration of L-dopa and 5-HTP to the patients with biopterin deficiency is necessary to prevent appearance of symptoms due to shortage of neurotransmitters.

Carbidopa is an inhibitor of aromatic amino acids decarboxylase. To administrate carbidopa with levodopa increase the amount of levodopa arriving at CNS to reduce degradation of L-dopa before blood-brain barrier. By using carbidopa and levodopa, total dose of levodopa for patients with PNDs could decrease. Other type of PNDs is due to dysfunction of GABA

metabolic system. In this manuscript, the author described SSADH deficiency. Previous reports described that an inhibitor of GABA transaminase improved their psychomotor dysfunction al least partially.

AADC deficiency is one of disorders that L-dopa is ineffective. Gene therapy has been expected to improve symptoms of these patients. To replace abnormal enzyme to normal enzyme is enable to convert L-dopa into dopamine in CNS and supplement of dopamine is expected to suppress involuntary movements.

Botulinum toxin therapy (A Pickett and R L Rosales. 2011) and deep brain stimulation (DBS) (K L Collins et al. 2010) have each been shown to be effective mangaement approaches in dystonia. Botulinum toxin is often used in focal dystonia and DBS is usually treated by general dystonia. Both two therapies have not been applied for PNDs because symptoms due to PNDs are often improved by administration of L-dopa. However, in severe patients or patients who are not response to L-dopa, those two therapies will be considered as an alternative therapies.

## 4. Acknowledgements

## 5. References

Allen GF, Land JM, Heales SJ. (2009) A new perspective on the treatment of aromatic L-amino acid decarboxylase deficiency. *Mol Genet Metab*. Vol. 97, No. 1, pp. 6-14.

Asada H, Kawamura Y, Obata K. (1997) Cleft palate and decreased brain gamma-aminobutyric acid in mice lacking the 67-kDa isoform of glutamic acid decarboxylase. *Proc Natl Acad Sci* Vol. 94, pp. 6496-6499.

Bandmann O, Nygaard TG, Harding AE. (1996) Dopa-responsive dystonia in British patients: new mutations of the GTP-cyclohydrolase I gene and evidence for genetic heterogeneity. *Hum Mol Genet*. Vol. 5, No. 3, pp. 403-6.

Bandmann O, Goertz M, Oertel W. (2003) The phenylalanine loading test in the differential diagnosis of dystonia. *Neurology*. Vol. 60, No. 4, pp.700-2.

Bernard G, Vanasse M, Chouinard S. (2010) A case of secondary dystonia responding to levodopa. *J Child Neurol*. Vol. 25, No. 6, pp. 780-1.

Biaggioni I and Robertson D. (1987) Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. *Lancet* Vol. 2, pp. 1170-1172.

Bonafé L, Thöny B, Blau N. (2001) Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-neurotransmitter deficiency without hyperphenylalaninemia. *Am J Hum Genet*. Vol. 69, No. 2, pp. 269-77.

Bräutigam C, Hyland K, Sharma R *et al*. (2002) Clinical and laboratory findings in twins with neonatal epileptic encephalopathy mimicking aromatic L-amino acid decarboxylase deficiency. *Neuropediatrics*. Vol. 33, No. 3, pp. 113-7.

Brun L, Ngu LH, Orcesi S. (2010)Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. *Neurology* Vol. 75, pp. 64-71.

Brunner HG, Nelen MR, van Oost BA. (1993) X-linked borderline mental retardation with prominent behavioral disturbance: phenotype, genetic localization, and evidence for disturbed monoamine metabolism. *Am. J. Hum. Genet*. Vol. 52, pp. 1032-1039.

Castaigne P, Rondot P, Said G. (1971) Progressive extrapyramidal disorder in 2 young brothers. Remarkable effects of treatment with L-dopa. *Rev Neurol* (Paris) Vol. 124, pp. 162–6.

Chaila EC, McCabe DJ, Murphy RP. (2006) Broadening the phenotype of childhood-onset dopa-responsive dystonia. *Arch Neurol*. Vol. 63, No. 8, pp. 1185-8.

K L Collins, E M Lehmann, P G Patil. (2010) Deep brain stimulation for movement disorders. *Neurobiol Dis*. Vol. 38, pp. 338-345

Freeman R and Landsberg L. (1991) The treatment of orthostatic hypotension with dihydroxyphenylserine. *Clin Neuropharmacol*. Vol. 14, pp. 296-304.

Fujioka H, Shintaku H, Yamano Y. (2009) Plasma phenylalanine level in dopa-responsive dystonia. *Mov Disord*. Vol. 24, No. 15, pp. 2289-2290.

Fujita S and Shintaku H. (1990) Etiology and pteridin metabolism abnormality of hereditary progressive dystonia with marked diurnal fluctuation [in Japanese]. *Med J Kushiro City Hosp* Vol. 2, pp. 64–67.

Furukawa Y, Nishi K, Kondo T, et al. (1993) CSF biopterin levels and clinical features of patients with juvenile parkinsonism. In: Narabayashi H, Nagatsu T, Yanagisawa N, et al. eds. *Advances in Neurology*. Vol 60, pp. 562–567, New York: Raven.

Furukawa Y, Lang AE, Trugman JM, et al. (1998) Gender-related penetrance and de novo GTP-cyclohydrolase I gene mutations in dopa-responsive dystonia. *Neurology*. Vol.50, pp. 1015-1020.

Furukawa Y, Nygaard TG, Gutlich M, et al. (1999) Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. *Neurology*. Vol. 53, pp. 1032-1041.

Furukawa Y, Kapatos G, Haycock JW, et al. (2002) Brain biopterin and tyrosine hydroxylase in asymptomatic dopa-responsive dystonia. *Ann Neurol*. Vol. 51, pp. 637-641.

Furusho U, Hirano Y, Hayashi K, et al. (1993) A familial case of juvenile parkinsonism presenting with dystonia with marked diurnal fluctuation at age 5 [in Japanese]. *Tokyo Joshi Ikadaigaku Zasshi (J Tokyo Women's Med Coll)* (Tokyo) Vol. 63, pp. 405–412.

Gibson KM, Nyhan WL, Jakobs C *et al*. (1983) Succinic semialdehyde dehydrogenase deficiency: an inborn error of gamma-aminobutyric acid metabolism. *Clin Chim Acta*. Vol. 133, No. 1, pp. 33-42.

Gibson KM, DeVivo DC, Jakobs C. (1989) Vigabatrin therapy in patient with succinic semialdehyde dehydrogenase deficiency. *Lancet*. Vol. 2, No. 8671, pp. 1105-6.

Gibson KM, Jakobs C, Hagenfeldt L *et al*. (1995) Vigabatrin therapy in six patientswith succinic semialdehyde dehydrogenase deficiency. *J Inherit Metab Dis*. Vol. 18, No. 2, pp. 143-6.

Gropman A. (2003) Vigabatrin and newer interventions in succinic semialdehyde dehydrogenase deficiency. *Ann Neurol*. Vol. 54 Suppl 6: pp. S66-72.

Hoffmann GF, Assmann B, de Klerk JB, et al. (2003) Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. *Ann Neurol*. Vol. 54 (Suppl 6) pp. S56–65.

Hyland K, Fryburg JS, Trugman JM. (1997) Oral phenylalanine loading in dopa-responsive dystonia: a possible diagnostic test. *Neurology*. Vol. 48, No. 5, pp. 1290-7.

Ichinose H, Ohye T, Takahashi E, et al. (1994) Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nat. Gen*. Vol. 8, pp. 236 –242.

Ide S, Kato M, Goto Y. (2010) Abnormal glucose metabolism in aromatic L-amino acid decarboxylase deficiency. *Brain Dev*. Vol. 32, No. 6, pp. 506-10.

Ito S, Ide S, Ito Y *et al*. (2008) Aromatic L-amino acid decarboxylase deficiency associated with epilepsy mimicking non-epileptic involuntary movements. *Dev Med Child Neurol*. Vol. 50, No. 11, pp. 876-8.

Jaeken J, Casaer P, Brucher JM et al. (1984) Gamma-aminobutyric acid-transaminase deficiency: a newly recognized inborn error of neurotransmitter metabolism. *Neuropediatrics* Vol. 15, pp. 165-169.

Jarraya B, Boulet S, Jan C *et al*. (2009) Dopamine gene therapy for Parkinson's disease in a nonhuman primate without associated dyskinesia. *Sci Transl Med*. Vol. 1, No. 2, pp. 2ra4

Korenke GC, Christen HJ, Hyland K. (1997) Aromatic L-amino acid decarboxylase deficiency: an extrapyramidal movement disorder with oculogyric crises. *Eur J Paediatr Neurol*. Vol. 1, No. 2-3, pp. 67-71.

Kusmierska K, Jansen EE, Szymanska *et al.* (2009) Sepiapterin reductase deficiency in a 2-year-old girl with incomplete response to treatment during short-term follow-up. *J Inherit Metab Dis*. Jan 7. [Epub ahead of print]

DE Lonlay P, Nassogne MC, van Cruchten AC *et al*. (2000) Tyrosine hydroxylase deficiency unresponsive to L-dopa treatment with unusual clinical and biochemical presentation. *J Inherit Metab Dis*. Vol. 23, No. 8, pp. 819-25.

Lüdecke B, Knappskog PM, Surtees RA *et al.* (1996) Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. *Hum Mol Genet*. Vol. 5, No. 7, pp. 1023-8.

Lynex CN, Carr IM, Markham A F et al. (2004) Homozygosity for a missense mutation in the 67 kDa isoform of glutamate decarboxylase in a family with autosomal recessive spastic cerebral palsy: parallels with stiff-person syndrome and other movement disorders. *BMC Neurol*. Vol. 4, No. 20,.

Manegold C, Hoffmann GF, Ikonomidou H et al. (2009) Aromatic L-amino acid decarboxylase deficiency: clinical features, drug therapy and follow-up. *J Inherit Metab Dis*. Vol. 32, No. 3, pp. 371-80.

McKnight K, Jiang Y, Lang B et al. (2005) Serum antibodies in epilepsy and seizure-associated disorders. *Neurology*. Vol. 65, No. 11, pp. 1730-6.

Medina-Kauwe LK, Tobin AJ, Gibson KM et al. (1999) 4-Aminobutyrate aminotransferase (GABA-transaminase) deficiency. *J. Inherit. Metab. Dis*. Vol. 22, pp. 414-427.

Nagata E, Segawa M, Fujioka H, *et al.* (2007) Dopa-responsive dystonia (Segawa disease) -like disease accompanied by mental retardation: a case report. *Mov Disord*. Vol. 22, No. 8, pp. 1202-3.

Neville BG, Parascandalo R, Felice A. (2005) Sepiapterin reductase deficiency: a congenital dopa-responsive motor and cognitive disorder. *Brain*. Vol. 128, Pt 10, pp. 2291-6.

Nygaard TG, Marsden CD, Duvoisin RC. (1988) Dopa-responsive dystonia. In: Fahn S, Marsden CD, Calne DB, eds. A*dvances in Neurology*. Vol. 50, pp. 377–384, New York: Raven.

Opladen T, Okun JG, Blau N. (2010) Phenylalanine loading in pediatric patients with dopa-responsive dystonia: revised test protocol and pediatric cutoff values. *J Inherit Metab Dis*. Vol. 33, No. 6, pp. 697-703.

Opladen T, Hoffmann G, Wolf N. (2011) Clinical and biochemical characterization of patients with early infantile onset of autosomal recessive GTP cyclohydrolase I deficiency without hyperphenylalaninemia. *Mov Disord*. Vol. 26, No. 1, pp. 157-61.

Pearce DA, Atkinson M, Tagle DA. (2004) Glutamic acid decarboxylase autoimmunity in Batten disease and other disorders. *Neurology*. Vol. 63, No. 11, pp. 2001-5.

Pearl PL, Taylor JL, Sokohl A. (2007) The pediatric neurotransmitter disorders. *J Child Neurol*. Vol. 22, No. 5, pp. 606-16.

Pearl PL, Shukla L, Gibson K et al. (2011) Epilepsy in succinic semialdehyde dehydrogenase deficiency, a disorder of GABA metabolism. *Brain Dev*. Jun 9. [Epub ahead of print]

A Pickett and R L Rosales. (2011) New Trends in the Science of Botulinum Toxin-A as applied in Dystonia. *International Journal of Neuroscience* Vol. 121, pp. 22–34

Pons R, Ford B, De Vivo DC. (2004) Aromatic L-amino acid decarboxylase deficiency: clinical features, treatment, and prognosis. *Neurology* Vol. 62, pp. 1058-1065.

Rating D, Hanefeld F, Kneer J *et al.* (1984) 4-Hydroxybutyric aciduria: a new inborn error of metabolism. I. Clinical review. *J Inherit Metab Dis*. Vol. 7 Suppl 1, pp. 90-2.

Robertson D, Haile V, Perry SE. (1991) Dopamine β-hydroxylase deficiency. A genetic disorder of cardiovascular regulation. *Hypertension*. Vol. 18, pp. 1-8.

Robertson D, Goldberg MR, Robertson RM. (1986) Isolated failure of autonomic noradrenergic neurotransmission. Evidence for impaired β-hydroxylation of dopamine. *New Engl J Med*. Vol. 314, pp. 1494-1497.

Rondot P and Ziegler M. (1983) Dystonia–L-dopa responsive or juvenile parkinsonism? *J Neural Transm Suppl*. Vol. 19, pp. 273–81.

Rondot P, Aicardi J, Ziegler M. (1992) Dopa-sensitive dystonia. *Rev Neurol* (Paris) Vol. 148, pp. 680–6.

Sato S, Chiba T, Kakiuchi T et al. (2006) Decline of striatal dopamine release in parkin-deficient mice shown by ex vivo autoradiography. *J Neurosci Res.* Vol. 84, No. 6, pp. 1350-7.

Segawa M, Ohmi K, Itoh S, et al. (1971) Childhood basal ganglia disease with remarkable response to L-dopa: hereditary basal ganglia disease with marked diurnal fluctuation [in Japanese]. *Shinryo* (Tokyo) Vol. 24, pp. 667– 672.

Segawa M, Hosaka A, Miyagawa F, et al. (1976) Hereditary progressive dystonia with marked diurnal fluctuation. In: Eldridge R, Fahn S, eds. *Advances in Neurology*. Vol. 14, pp. 215–233, Raven, New York

Segawa M, Nomura Y, Nishiyama N. (2003) Autosomal dominant guanosine triphosphate cyclohydrolase I deficiency (Segawa disease). A*nn Neurol.* Vol. 54 (Suppl 6), pp. S32-45.

Shintaku H. (2002) Disorders of tetrahydrobiopterin metabolism and their treatment. *Curr Drug Metab* Vol. 3, pp. 123-131.

Shintaku H, Kure S, Ohura T et al. (2004) Long-term treatment and diagnosis of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. *Pediatr Res*. Vol. 55, No. 3, pp. 425-30

Swoboda KJ, Hyland K, Levy HL. (1999) Clinical and therapeutic observations in aromatic L-amino acid decarboxylase deficiency. *Neurology*. Vol. 53, No. 6, pp. 1205-11.

Swoboda KJ and Hyland K, (2002) Diagnosis and treatment of neurotransmitter-related disorders. *Neurol Clin*. Vol. 20, pp. 1143-1161

Swoboda KJ, Saul JP, Hyland K. (2003) Aromatic L-amino acid decarboxylase deficiency: overview of clinical features and outcomes. *Ann Neurol*. Vol. 54 Suppl 6, pp. S49-55.

Tarsy D and Simon DK. (2006) Dystonia. *N Engl J Med.* Vol. 355, pp. 818-829.

Tassin J, Dürr A, Brice A et al., (2000) Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? *Brain*. Vol.123, Pt 6, pp. 1112-21

Tormenti MJ, Tomycz ND, Tyler-Kabara EC. (2011) Bilateral subthalamic nucleus deep brain stimulation for dopa-responsive dystonia in a 6-year-old child. *J Neurosurg Pediatr*. Vol. 7, No. 6, pp. 650-3.

Turjanski N, Bhatia K, Brooks DJ. (1993) Comparison of striatal 18F-dopa uptake in adult-onset dystonia-parkinsonism, Parkinson's disease, and dopa-responsive dystonia. *Neurology*. Vol. 43, No. 8, pp. 1563-8.

Watanabe T, Matsubara S, Suzuki M. (2009) Successful management of pregnancy in a patient with Segawa disease: case report and literature review. *J Obstet Gynaecol Res*. Vol. 35, No. 3, pp. 562-4.

Willemsen MA, Verbeek MM, de Rijk-van Andel JF *et al. (*2010) Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. *Brain*. Vol. 133, Pt 6, pp. 1810-22.

Yamakawa Y, Nakazawa T , Shimizu T. (2011) A boy with a severe phenotype of succinic semialdehyde dehydrogenase deficiency. *Brain Dev*. May 23. [Epub ahead of print]

Yosunkaya E, Karaca E, Yüksel. (2010) A Marked improvement in Segawa syndrome after L-dopa and selegiline treatment. *Pediatr Neurol*. Vol. 42, No. 5, pp. 348-50.

Zirn B, Steinberger D, Müller U. (2008) Frequency of GCH1 deletions in Dopa-responsive dystonia. *J Neurol Neurosurg Psychiatry*. Vol. 79, No. 2, pp. 183-6.
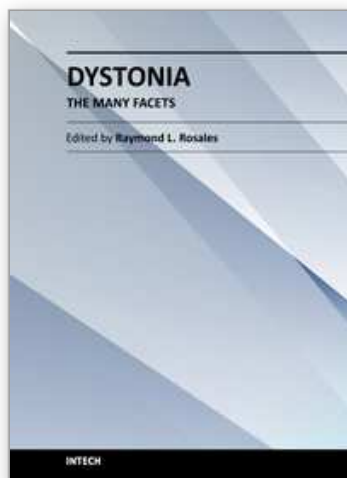
**Dystonia - The Many Facets**

Edited by Prof. Raymond Rosales

Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

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