Dopa-Responsive Dystonia : A syndrome of selective nigrostriatal dopaminergic deficiency

Dopa-responsive dystonia (DRD) is no longer a rare oddity. For the clinician, DRD poses a diagnostic challenge as its clinical presentation can be quite diverse. Marked and sustained response to L-dopa is the most crucial and absolute hallmark in confirming a diagnosis. Absence of degenerative nigral cell loss underlies the remarkable L-dopa response. The broadening spectrum of the clinical presentations, progress in molecular genetics with evidence of incomplete penetrance and phenotypic variability, biochemistry, utility of nuclear imaging in differential diagnosis, and treatment are discussed. I propose the concept of DRD as a syndrome, defined as selective nigrostriatal dopamine deficiency caused by genetic defects in dopamine synthesis without degenerative cell loss. I further propose the term DRD-plus, defined as inherited metabolic disorders which have symptomatic features of DRD, and those features not seen in DRD as well.

Key Words : *Dopa-Responsive Dystonia, Dopamine Transporter, Parkinson disease, GTP cyclohydrolase I, neopterin*

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Received : August 4, 1997
Accepted : August 4, 1997

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INTRODUCTION

Dopa-responsive dystonia (DRD) as a diagnostic entity is relatively recent. The first description of a patient with what is now known DRD was made by Beck in 1947 (1). An 8.5-year old girl was described as "kicking up her left heel on walking", which began about one year earlier. The right side became similarly affected. Within six months, the young girl could walk only with support. It was thought that she suffered from hysteria. On examination, she had generalized dystonia and tremor. Her face was described as expressionless, and her gait unsteady. It was also noted at that time that she had a 39-year old paternal uncle who had difficulty in walking at the age of 8, which became progressively worse. Beck's diagnosis : "dystonia musculosum deformans", a term for idiopathic torsion dystonia (ITD). Later Corner (1952) (2) examined the same girl, and noted worsened symptoms. Specifically, the young girl's symptoms were diurnal, and the symptoms responded dramatically to trihexyphenidyl. The girl's younger brother was similarly affected. However, Beck's diagnosis remained : a "typical case of dystonia musculosum deformans".

It is Segawa who deserves credit in recognizing DRD as a new entity. In 1972, Segawa et al. (3) reported two female cousins who presented with clumsiness, gait disturbance and fatiguability at age 4 and 6.5, respectively. Segawa emphasized the significance of the marked diurnal fluctuations, i.e., symptoms became worse as the day progressed. Most importantly, Segawa noted the marked L-dopa response. Segawa's report appeared to be substantially different from previously described dystonia, and thus the cases noted were first thought to be indigenous to Japan. When the clinicians tried L-dopa in their dystonic patients, L-dopa produced a dramatic response in some of the patients. It was only then that they realized that the Beck's case was DRD.

DRD has been described worldwide under different names : dystonia musculosum deformans (1, 4) ; progressive dystonia with marked diurnal fluctuation (5) ; fluctuating dystonia (6) ; dystonia with marked diurnal fluctuation (7) ; idiopathic dystonia-Parkinsonism with marked fluctuation of symptoms (8) ; hereditary progressive dystonia (9) ; dopa-sensitive progressive dystonia of childhood with fluctuations of symptoms (10) ; hereditary dystonia-parkinsonism syndrome of juvenile onset (11) ; autosomal dominant torsion dystonia (12) ; and then dopa-responsive dystonia (13). "Diurnally fluctuating hereditary progressive dystonia" was the term used when two families were reported at Seoul National University Hospital (14).

Recent description, uncommon occurrence, and lack of the simple common term led to poor awareness, and perhaps underdiagnosis. It is important to make the

diagnosis because the diagnosis assures the effective treatment. In this review, the clinical features, as well as the molecular genetics, pathology, laboratory studies, differential diagnosis, and treatment will be discussed.

CLINICAL PRESENTATION

Since the original description of "hereditary basal ganglia disease with marked diurnal fluctuation" (3), Segawa has maintained that "hereditary progressive dystonia with marked diurnal fluctuation" (HPD) is a separate entity from DRD. Segawa and Nomura's criteria for HPD (15) include: childhood onset; generalized postural dystonia; diurnal fluctuation; and marked and sustained benefit from L-dopa without unfavorable side effects. The patient should have preserved locomotor activity even in the advanced stage. Postural tremor is allowed within the criteria, but parkinsonian rest tremor is not. Similarly, freezing or march a petit pas, axial torsion, and action dystonia are exclusionary diagnostic criteria. The strict diagnostic criteria for HPD assure not to mistakenly diagnose juvenile Parkinson disease (JPD) as HPD (JPD is defined as Parkinson disease (PD) with onset before age 20).

However, many investigators believe that the diagnostic criteria for HPD are too restrictive, and that HPD and DRD actually are the same disease. Family studies of patients meeting the diagnostic criteria for HPD showed that the clinical features of the affected members were much broader (10, 16) than were dictated by Segawa. Assuming that the neurologically impaired patients in the family have the same disorder, the clinical spectrum and criteria of HPD needed to be modified.

The marked and sustained L-dopa response was the most unique characteristic that reliably separated the entity from other disorders, thus the term Dopa-Responsive Dystonia was coined (13). The L-dopa response proved to be the most crucial and absolute hallmark for the diagnosis of DRD. Family studies showed that other inclusion and exclusion criteria for the diagnosis of HPD were neither absolute, nor specific. Therefore, these criteria were dropped in the diagnostic criteria for DRD. For example, diurnal fluctuations, the very characteristic which led to the recognition of HPD, were shown to be neither absolute, nor specific. There were affected members with and without fluctuations within the same family (10, 16~18), which indicates that diurnal fluctuations are not absolute, and should not be a requirement for the diagnosis. Diurnal fluctuations were neither specific, and were frequently seen in ITD, JPD, and other disorders as described below. Parkinsonism such as rest tremor is exclusionary in Segawa's criteria for HPD. However, many clinicians believe that parkinsonian features are present in most cases who otherwise meet the criteria for HPD. Furthermore, family studies show that parkinsonism may actually be the sole manifestation of DRD (16,19). Therefore separation of HPD from DRD is artificial. In this review, we lump HPD and DRD as one disorder.

The clinical presentation of DRD falls into two major categories depending on age of onset: 1) classic DRD of childhood onset, and 2) parkinsonism with onset in adulthood (20).

Childhood onset

This is the prototype of DRD and most common. Manifestations are diverse. Dystonia begins in the leg (demonstrating preference to the left side), which affects gait. Parkinsonism appears concurrently or later in most patients. Diurnal fluctuation is common (75%, varying in degree), but is not absolute. "Pyramidal tract signs" such as hyperreflexia, spasticity, and intermittent unsustained ankle clonus with upgoing toes may appear. However, corticospinal tract activity, measured by magnetic stimulation of the motor cortex, is normal (17), which suggests that these "pyramidal tract signs" have a extrapyramidal basis. Over half of the patients develop axial manifestations such as increased lumbar lordosis, scoliosis or torticollis. Generalized dystonia appears in most patients.

Adulthood onset

Parkinsonism may be the sole manifestation in adulthood onset DRD. Coincidental PD is not the cause for parkinsonism in DRD. The incidence of parkinsonism in the first degree relatives of DRD over the age 40 is much higher (14%) than that of normal control (0.6%). Parkinsonism in DRD is different from that of PD: the L-dopa dose is very small (100~300 mg/d), and does not need to be increased. Quality of improvement with L-dopa is much better in parkinsonism of DRD. Additionally, neither fluctuations nor dyskinesia appear with long-term L-dopa treatment in parkinsonism of DRD, which is common in PD and more so in JPD. Furthermore, fluorodopa positron emission tomography (PET) shows differences in fluorodopa uptake. Fluorodopa uptake was normal in 2 females who had adult-onset parkinsonism and were relatives of DRD (19). In contrast, fluorodopa uptake was decreased in PD (21) and JPD (22~24).

Uncommon presentations

Although most patients have normal developmental

milestones, some have had unexplained motor delays preceding overt dystonia (20, 25). Some patients have actually been misdiagnosed with cerebral palsy (26, 27). Two patients at Seoul National University Hospital were diagnosed as spastic cerebral palsy and developmental motor delay, respectively (personal observation). Clinical elements of "pyramidal tract signs" may dominate the picture without overt dystonia, misleading the clinicians to the diagnosis of hereditary spastic paraparesis (28, 29). There are some DRD cases who have oculogyric crisis (4, 10, 11, 13, 30, 31). Other unusual presentations include a report of L-dopa responsive kyphoscoliosis (32). Therefore, it is important to consider the diagnosis of DRD in every children with unexplained motor delays or cerebral palsy, and other unusual motor disturbances. Please see the illustrative cases in the Appendix.

INHERITANCE

Autosomal dominant inheritance with reduced penetrance is the most common form of DRD. Penetrance is sex-related, and is estimated as 15% in men and 45% in women (20). Penetrance may be higher if incomplete presentations are included (16). Sporadic cases of DRD are believed to be from reduced penetrance. Mutations in the GTP cyclohydrolase I (GCH-I) gene have been found in some but not all patients (33~38). A German family with mutation in the TH gene is reported, which is autosomal recessive (39).

PATHOLOGY

Although there are severe motor disabilities, often leading to a nonambulatory state, DRD is not fatal. Therefore, pathological examination has been limited to one patient (40). The patient (originally reported in (4)) presented with difficulty in walking at age 5. By age 8, dystonia was generalized. Levodopa 750 mg/d normalized her motor deficit completely for 11 years until her death at age 19 by a motor vehicle accident. Pathological examination of the patient showed no evidence of degenerative process in the substantia nigra and striatum. There were no cell loss, gliosis and abnormal inclusion bodies such as Lewy body. Normal numbers of hypopigmented nigral neurons, normal TH immunoreactivity, and TH protein were seen in the substantia nigra. However, TH protein, TH activity, and dopamine level were reduced in the striatum, and the loss was more pronounced in the putamen than the caudate, as seen in PD. Dopamine transporter density measured by GBR 12,935 was within normal range.

Pathological examination of JPD are also very rare, and the findings differ from DRD. In 1984, Yokochi et al. (41) reported the pathology of a 39-year old woman who began to have walking difficulty, with tendency to fall at age 6. She demonstrated a good response to L-dopa, but developed dyskinesia after one year. Initial pathological examination described hypopigmented, "immature"-appearing cells in the nigra, which were "almost normal" in number. However, reevaluation of the material demonstrated severe cell loss in the ventrolateral portion of the substantia nigra pars compacta, and there were Lewy bodies in the remaining neurons (42). Also, Olsson et al. (43) reported a 23-year old woman who was first diagnosed as having DRD at age 12, but pathological examination showed pronounced gliosis, loss of nigral neurons, and presence of Lewy bodies. This case is an example of JPD mistaken as DRD.

LABORATORY STUDIES

Routine laboratory studies are conspicuously normal, as are CT and MRI. CSF homovanillic acid is decreased (5, 7, 9), but normal levels are also described (8). The fluorodopa PET study, dopamine transporter imaging, and CSF neopterin measurement are most informative. Molecular genetic studies can be done at the research level. A work-up for Wilson disease may be considered in order to rule out this fatal, but treatable condition.

Fluorodopa PET

The fluorodopa PET study examines a complex of decarboxylation, vesicular uptake and storage of fluorodopa, and provides in vivo information of presynaptic nigrostriatal dopaminergic neurons. Fluorodopa uptake is decreased in PD (21) and in JPD (22, 24), which is consistent with nigrostriatal neuronal loss and reduced dopaminergic storage. In contrast, fluorodopa uptake is normal in DRD (22~24).

Dopamine transporter imaging

Dopamine transporter imaging has proved to be a reliable and sensitive test for PD (44~48). Dopamine transporter is a protein located in the dopaminergic nerve terminals (49). Dopamine transporter imaging measures the density of dopamine transporter in the striatum, and thus examines the integrity of the nigrostriatal dopaminergic nerve terminals. There is a degenerative loss of the nigral cells, and a decrease in the dopaminergic nerve terminals and dopamine transporter in the striatum in PD and JPD. In contrast to PD and JPD, there is no

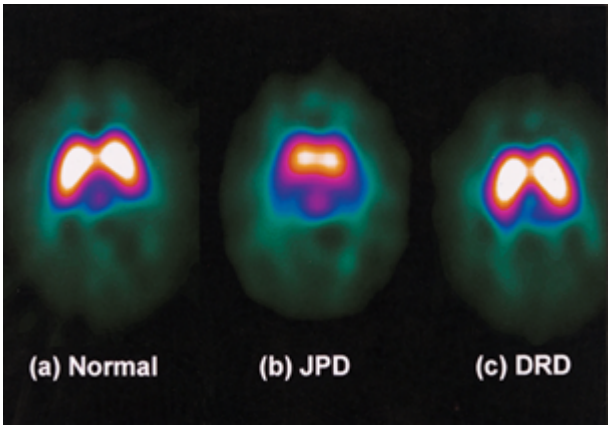

Fig. 1. [^{123}I]-β-CIT SPECT images of a normal control, DRD and JPD. [^{123}I]-β-CIT striatal binding is very high in the 20-year-old normal control (a), and 30-year-old DRD patient (c). In sharp contrast, it is markedly decreased in the 17-year-old JPD patient (b).

nigral cell loss, and dopamine transporter is normal in DRD (40). Thus, dopamine transporter imaging is helpful in differentiating DRD from PD and JPD (38) (Fig. 1).

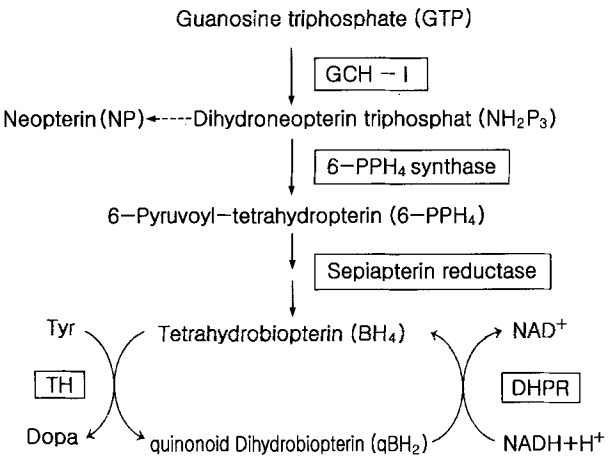

Fig. 2. The biosynthetic pathway of tetrahydrobiopterin (BH_4) from guanosine triphosphate (GTP). BH_4 is a cofactor of tyrosine hydroxylase (TH). TH is the rate-limiting enzyme in the dopamine synthesis. GTP cyclohydrolase I (GCH-I) is the initial and rate-limiting step in the synthesis of BH_4. Therefore, decrease in TH or GCH-I activity results in decreased dopamine synthesis. Neopterin is a degradation product of dihydroneopterin triphosphate, which is the intermediate formed by GCH-I. Therefore, neopterin level indirectly reflects the GCH-I activity. 6-Pyruvoyl-tetrahydropterin synthase (6-PPH_4 synthase), sepiapterin reductase and dihydropteridine reductase (DHPR) are other enzymes in the BH_4 metabolism. Defects in 6-PPH_4 synthase and DHPR have been reported to cause dystonia responsive to L-dopa (see text for details).

Neopterin

Neopterin is a byproduct of dihydroneopterin triphosphate, which is the first intermediate in the biosynthesis of tetrahydrobiopterin (BH_4) from GTP (Fig. 2). Dihydroneopterin triphosphate is formed from GTP by GCH-I. Therefore, CSF neopterin reflects the activity of GCH-I. Mutations in the GCH-I gene in DRD decrease formation of dihydroneopterin triphosphate and neopterin. CSF neopterin was measured in 5 DRD patients, and the levels were markedly low in all of them (personal observation). The mutation in the GCH-I gene was found in one patient (38) (Fig. 3). However, complete sequencing of all the 6 exons of the GCH-I gene in 3 other patients did not show any mutation (data not shown). Therefore, CSF neopterin measurement may be useful to diagnose DRD when sequencing does not identify mutations. CSF neopterin may be useful to differentiate from other defects in BH4 biosynthesis such as in dihydropteridine reductase (DHPR) and 6-pyruvoyl-tetrahydropterin synthase (6-PPH_4 synthase) (Fig. 2). Both DHPR and 6-PPH_4 synthase deficiencies may present with diurnally fluctuating dystonia, and may partially respond to L-dopa (See section VI. Differential diagnosis). CSF neopterin levels increase in DHPR and 6-PPH_4 synthase deficiencies. CSF neopterin in DRD from TH mutation has not been measured.

Molecular genetic study

A mutation in the TH gene was reported in an autosomal recessive form of DRD (39). Most mutations for the disease have been found in the GCH-I gene (33~38). The GCH-I is the initial and rate-limiting enzyme in the synthesis of BH_4 (Fig. 2). Tetrahydrobiopterin (BH4) is a cofactor for TH. Therefore, mutations in the GCH-I gene limit the formation of L-dopa from tyrosine.

A novel nonsense ($Ser^{114}Ter$) mutation in the exon 1 of the GCH-I gene was found in one of our families (38) (Fig. 3). CSF neopterin was decreased, which is an indirect evidence for decreased activity of GCH-I, and supports that the mutation is functionally significant. The mutation in the GCH-I gene in the affected members was heterozygous consistent with autosomal dominant inheritance. There were three obligate carriers in the pedigree (I-1,2, and II-1 in Fig. 3). The gene carrier state was confirmed by sequencing in two of them (Gene study was not done in I-1) (Fig. 3). Two young boys (III-2,4) had the mutation, but neither had symptoms. This may be an example of sex-related penetrance. There are two types of DRD presentations in this family: typical childhood onset dystonia in four, and cerebral palsy in one. Both types have the same mutation, which

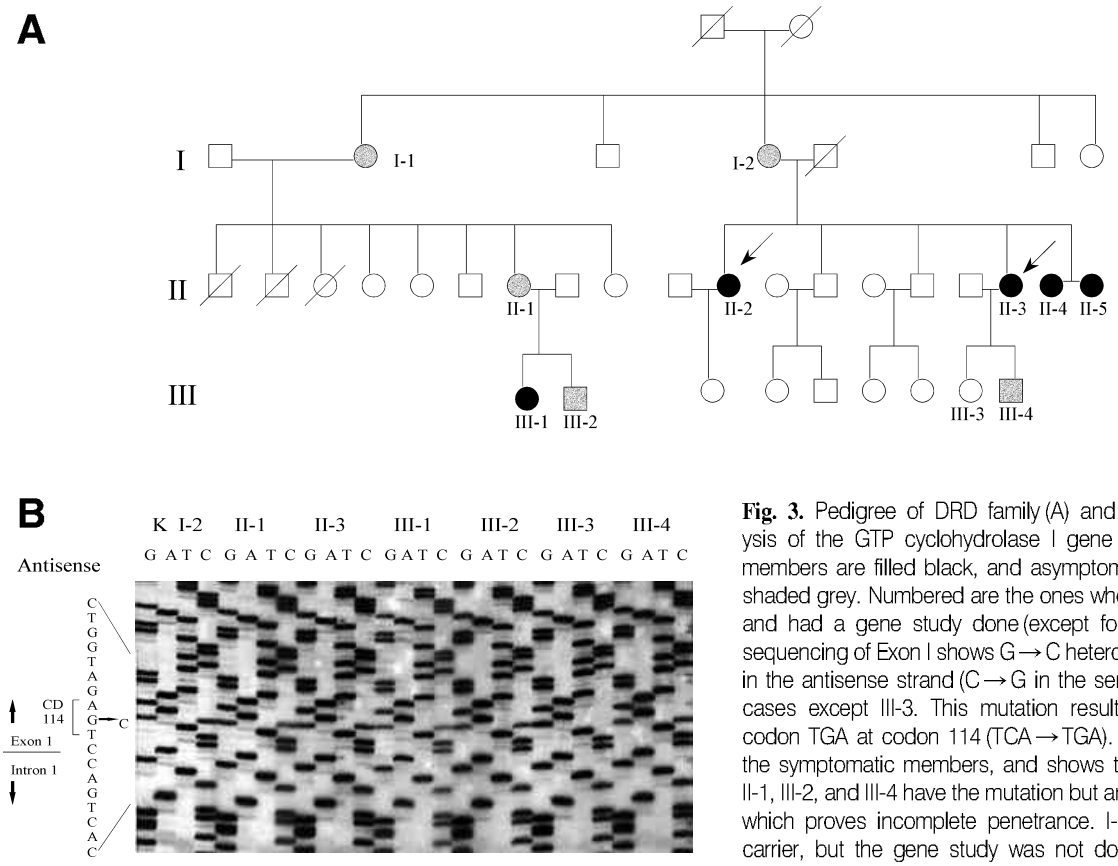

Fig. 3. Pedigree of DRD family (A) and sequence analysis of the GTP cyclohydrolase I gene (B). (A) Affected members are filled black, and asymptomatic carriers are shaded grey. Numbered are the ones who were examined and had a gene study done (except for I-1). (B) Direct sequencing of Exon I shows G → C heterozygous mutation in the antisense strand (C → G in the sense strand) in all cases except III-3. This mutation results in termination codon TGA at codon 114 (TCA → TGA). II-3 and III-1 are the symptomatic members, and shows the mutation. I-2, II-1, III-2, and III-4 have the mutation but are asymptomatic, which proves incomplete penetrance. I-1 is an obligate carrier, but the gene study was not done.

is a genetic evidence for phenotypic variability.

Phenylalanine loading test

Phenylalanine is metabolized into tyrosine by phenylalanine hydroxylase in the liver and kidney. BH_4 is a cofactor for phenylalanine hydroxylase. Patients with autosomal recessive defects in BH_4 biosynthesis presents with hyperphenylalaninemia (50). Although DRD has a defect in synthesis of BH_4, there are no known DRD patients who have hyperphenylalaninemia. However, when phenylalanine was orally loaded in DRD patients, blood phenylalanine level increased to a higher level than in normal controls, with slow clearance of phenylalanine from blood and decreased production of tyrosine (52). This abnormality was corrected by pretreatment with BH_4. The data indicate that patients with DRD have sufficient systemic BH_4 store to metabolize normal intake of phenylalanine, but insufficient BH_4 store and synthetic capacity to metabolize a high phenylalanine load. The test may be useful in metabolically screening DRD patients, and in diagnosing DRD when mutation is not demonstrable. However, it should be noted that phenylalanine load test is abnormal in defects of BH_4 biosynthesis other than GCH-I. The test has not been done in DRD patients with TH mutation.

DIFFERENTIAL DIAGNOSIS

Major differential diagnosis for DRD includes ITD, JPD, and cerebral palsy.

ITD

The presence of parkinsonism, marked sustained response to L-dopa, and decreased CSF neopterin in DRD should help to differentiate from ITD (20). ITD with marked response to small doses of anticholinergics and L-dopa were later shown to be DRD (1,4). Onset age, presence or absence of diurnal fluctuation, axial torsion and action dystonia (15) are not reliable in differential diagnosis (13).

JPD

Differentiation of DRD from JPD is the most problematic. JPD usually begins with foot dystonia, rigidity, slowness, and variable to absent tremor (18). JPD may have diurnal fluctuations (8, 52~55, personal

observation). Many JPD patients are familial (18, 54, 56 ~57). JPD occurs slightly later than DRD. There is no female predominance as seen in DRD. JPD may show a good response to small doses of L-dopa in the early stage. However, this response declines with time. There is an early development of wearing off and dyskinesia (56 ~62, personal observation). Until the L-dopa benefit declines, the diagnosis remains uncertain, and misdiagnosis is common (summarized in (20)).

Fluorodopa PET study, dopamine transporter imaging, and CSF neopterin measurement help in making the diagnosis. For example, case 7 of "atypical DRD" in Sawle et al. (22) demonstrates the usefulness of fluorodopa PET study. The patient closely resembled DRD early in the illness, and was reported as such (6, 10). However, the dose of L-dopa needed to be increased, and fluctuation and dyskinesia appeared during follow up. Fluorodopa PET study showed a major reduction of fluorodopa uptake, which was clearly different from other DRD cases. Thus, the diagnosis of JPD was confirmed. In respect to dopamine transporter imaging, striatal dopamine transporter density, when measured by (^{123}I)-β -CIT binding, was severely decreased in JPD and PD, whereas it was normal in DRD (38) (Fig. 3).

CSF neopterin measurement is another test that may be useful.. Neopterin is severely decreased in DRD, but not in JPD (34, 57). Phenylalanine loading test may help by showing normal phenylalanine clearance in JPD, but no study has been done.

Cerebral palsy

At least 16 out of 66 cases were initially misdiagnosed as cerebral palsy (18). In early onset DRD, motor delays and clinical signs of spasticity may dominate the clinical picture without obvious dystonia. When the cause for the motor deficit is not clear, a diagnostic trial of L-dopa is indicated.

Other inherited metabolic disorders

There are reports of defects in BH_4 synthesis which resemble DRD : deficiencies in DHPR (Nomura et al. at the Third International Dystonia Symposium, 1996) and 6-PPH_4 synthase (63~65) presented with dystonia which was responsive to L-dopa. Patients with 6-PPH_4 synthase deficiency were also noted to have marked diurnal fluctuations (63, 65). Homozygous GCH-I deficiency (usual symptoms : severe mental retardation, seizures, muscle hypertonia, and episodic hyperthermia) may present with dystonia (Hyland and Nomura et al. at the Third International Dystonia Symposium, 1996). Aromatic L-amino acid decarboxylase (AADC) deficiency also resembles DRD. The reported twins with AADC deficiency showed developmental delays, generalized hypotonia, oculogyric crisis (66), and diurnal fluctuations (personal communication by Dr. Blair Ford), all of which can be seen in early-onset DRD. The twins also showed some features of autonomic instability such as abnormal pupillary reactions, orthostatic blood pressure change, and temperature instability.

These inherited metabolic disorders are autosomal recessive in inheritance, whereas DRD is autosomal dominant in most cases. Even though these metabolic disorders may resemble DRD, there are two features that set them apart from DRD. In contrast to DRD, neurologic symptoms are not limited to motor system, and include nonmotor symptoms such as mental retardation, seizures, and autonomic instability as well. Furthermore, neurologic deficits are only partially reversed by L-dopa. All these metabolic disorders affect dopamine synthesis. Dopamine deficiency in these disorders may underlie dystonia, and response to L-dopa, therefore giving resemblance to DRD. However, the neurochemical deficits in these metabolic disorders are more widespread than just involving dopamine as in DRD. The widespread neurochemical deficits may underlie nonmotor symptoms, and may be the cause of incomplete reversal by L-dopa.

TREATMENT

Small dose of L-dopa is the most effective medication (up to 20 mg/Kg/d when given without AADC inhibitors). Temporary choreic movements may appear by rapid increase of dose or overmedication, and are quickly reversible (67) (See patient 2 in the Appendix). The benefit should continue without the need for increase in dose, or the appearance of L-dopa related complications. L-dopa was very effective even when tried up to 52 years after the onset of the illness (68). Patient between the ages of 11.7 and 14.7 may report subjective feelings of ineffectiveness. This occurs from 2 months to 8.6 years after treatment. These feelings are not reported in patients with onset after midteens, and are quickly improved by increasing L-dopa or by adding AADC inhibitors (67).

Bromocriptine is effective, but does not afford complete relief (7, 8, 69). As in the case of Corner (2), anticholinergics such as trihexyphenidyl may have marked and prolonged benefit (70). However, L-dopa is preferred by the patients (67, personal observation). The benefit of anticholinergics may be through the dopamine reuptake blockade (71), rather than cholinergic receptor blockade. NMDA antagonistic action may also play a

role. Amantadine was found to be effective (8). Carbamazepine did not give consistent response in a few tried (18). Carbamazepine is a weak dopamine reuptake blocker (72). Benefit of BH_4 was not consistent (73~75).

Also of note, there has been no adverse effects reported related to the use of L-dopa with dopa decarboxylase inhibitors during pregnancy (76~78). Our DRD patients had 3 normal deliveries while on L-dopa and benserazide (personal observation).

CONCLUSION

Until now, DRD has been a clinical diagnosis. The clinical features are broad, and are not specific enough to make a confirmatory diagnosis. The dramatic and sustained L-dopa response can confirm the diagnosis, however, it requires a long-term follow up. Therefore the clinical diagnosis of DRD in new patients may be uncertain, and remain so for a long time.

The genetic diagnosis of DRD is neither simple nor practical. Until now, no common mutations have been found in the GCH-I gene (33~38). Therefore it is necessary to fully sequence the entire gene to detect possible mutations. Moreover, mutations may not be found in the GCH-I gene in some patients (33, 35, personal observation). Although mutations were not found in the GCH-I gene in one family and in a sporadic case (38), CSF neopterin was decreased in these patients, which suggests that there is a functional mutation. A family of DRD with a mutation in the TH gene raises the possibility that there may be other candidate genes. Reports that the defects in DHPR, 6-PPH_4 synthase and AADC have some clinical features similar to DRD make this possibility a real one.

Therefore, we propose the definition of DRD as a syndrome of selective nigrostriatal dopamine deficiency caused by genetic defects in the dopamine synthetic pathway without nigral cell loss. This definition assumes all the known clinical, biochemical, genetic and pathological information on DRD. Our definition of DRD is not only simple but also practical, needing only clinical information and dopamine transporter imaging.

We further propose the term DRD-plus, defined as inherited metabolic disorders which have symptomatic features of DRD, and those features not seen in DRD

Table. Differential diagnosis of DRD

	ITD[a]	JPD[b]	DRD[c]	DRD-plus[d]
Symptoms and signs				
Motor symptoms				
dystonia	+	+	+	+
parkinsonism	−	+	+/−	−[3]
Nonmotor symptoms[1]	−	−	−	−
Systemic symptoms[2]	−	−	−	−
Laboratory tests				
Fluorodopa PET	Normal	Abnormal	Normal	Normal[4]
Dopamine transporter imaging	Normal	Abnormal	Normal[5]	Normal[4]
CSF Neopterin	Normal	Normal	Reduced[6]	Abnormal[7]
Phenylalanine loading test	Normal[4]	Normal[4]	Abnormal[6]	Abnormal[8]
L-dopa response				
dose	Large	Small[9]	Small	Large
response degree	Minimal	Good	Marked	Partial
long-term complication	Absent	Frequent	Absent	Absent[4]

a : Idiopathic torsion dystonia
b : Juvenile Parkinson disease
c : Dopa-responsive dystonia
d : See definition in the text. Currently, includes homozygous GCH-I, DHPR, 6-PPH_4 synthase, and AADC deficiencies.
1 : mental retardation, seizures, autonomic instability, lethargy, irritability, hypersalivation, microcephaly.
2 : physical retardation, rash, eczema, pneumonia, sudden death.
3 : Not recorded, but expected to be present in some.
4 : No data yet. Based on prediction.
5 : Our data suggest that dopamine transporter may be upregulated in DRD.
6 : No data on DRD with TH mutation.
7 : Increased in DHPR and 6-PPH_4 synthase deficiency. Decreased in homozygous GCH-I deficiency. Expected to be normal in AADC deficiency.
8 : No data in AADC deficiency.
9 : Need gradual increase.

as well. A comparable example of nomenclature may be seen in the case of PD and Parkinson-plus. Homozygous GCH-I, DHPR, 6-PPH_4 synthase, and AADC deficiencies all fall under the umbrella of DRD-plus. In addition to clinical features, L-dopa response is another important hallmark in distinguishing DRD and DRD-plus : L-dopa reverses neurologic deficits completely in DRD ; and only partially in DRD-plus. Using L-dopa response as a differential diagnostic point is again analogous to the situation in PD and Parkinson-plus. However, the dichotomy may not always be clear-cut. Heterozygous GCH-I mutations have a selective nigrostriatal dopamine deficiency syndrome (which is DRD). However, there may be cases of heterozygous GCH-I mutation which have extreme loss of GCH-I activity, and affect other neurotransmitter systems in addition to nigrostriatal dopaminergic system. In these cases, DRD-plus would be the diagnosis, although the genetic defects are the same as in DRD. On the other hand, there may be cases which behave like DRD, but have mutations in the genes that usually cause DRD-plus syndrome. The features of AADC deficiency (66) closely resembled DRD in the early stage, and the differential diagnosis would have been difficult without close follow-up examination of the patients, L-dopa trial, and laboratory investigation. This overlap between DRD and DRD-plus is again similar to the clinical reality in PD and Parkinson-plus (See Table for framework of differential diagnosis).

Progress in pathology, biochemistry, nuclear imaging, and molecular genetics has contributed to the understanding of the basic pathophysiology of DRD. However, there are many questions that remain to be answered : Why are there the sex-related penetrance, side preference to the left, specific age of onset, and (age-related) phenotypic variability? What is the functional mutation in DRD? BH_4 has multiple physiological functions. It is a cofactor not only for TH, but also for phenylalanine and tryptophan hydroxylases which form norepinephrine, epinephrine and serotonin. BH_4 is suggested in the proliferation and growth of erythroid cells. How then does the mutation in the GCH-I gene results in selective nigrostriatal dopamine deficiency? Furthermore, the rostrocaudal pattern of decrease in dopamine level in the striatum is quite similar to the pattern in PD. This finding too, requires further study.

DRD is a diagnosis which may arise in a variety of clinical settings. If the diagnosis is confirmed, the patient can be saved from an unrelentingly progressive neurologic disability. The diagnosis and treatment of this disorder provides a truly rewarding experience for clinicians. A trial of L-dopa is safe, and should be encouraged, especially when the diagnosis is unclear.

Acknowledgements

This study was in part supported by the Korea Science Foundation (95-0403-96-3). I would like to thank Professors JM Jeong, SS Park, DS Lee, MC Lee, and SB Lee, and other people at Seoul National University Hospital whose collaboration was essential in doing the studies related to this review. I also acknowledge that the gene study was done with generous help from Drs. Segawa and Tsuji in Japan. I would like to express special thanks to Rev. Peregrine Murphy for giving the most diligent grammatical correction of the manuscript. However, the author is responsible for the final revision.

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APPENDIX

Patient 1

This 26-year-old female began to have left foot bending down and turning in after a dancing class in the afternoon at age 12. Abnormal posturing of the left foot caused limping, and disappeared after 2~3 hours of rest. In about 4 years, right foot dystonia, and clumsiness on both hands developed. Neck turning to right, trunk leaning to right, writing and walking difficulty developed later. There were marked diurnal fluctuations, being almost normal in the morning and sometimes nearly wheelchair bound in the late afternoon. A couple of days rest relieved many of her symptoms even in the afternoon. Even with this physical handicap, her academic performance was in the top level. She was a product of normal pregnancy and delivery. Early developmental milestones were normal. When first seen at age 17 with her similarly affected younger sister, there was tight fisting of both hands, equinovarus posturing of the left foot, leg spasticity with increased knee and ankle jerks, bradykinesia and postural instability. L-dopa 1500 mg/d was given with remarkable relief of symptoms. Later, L-dopa was changed to L-dopa/benserazide 100 mg/d. She has been completely free of any symptoms for 9 years without drug related complications.

Patient 2

This 8-year-old maternal cousin of Patient 1 was diagnosed as having spastic cerebral palsy at age 2, and had been managed as such. Her mother heard about her cousins, and brought her to us at age 4. She was a product of uneventful pregnancy and delivery. She could control her head at 3 months, crawl at 6 months, and stand at 11 months. However, it was noted that she tended to waddle with tiptoeing when she began to walk at 13 months. Examination at age 2 was recorded as that she had equinus posturing of the left foot with increased ankle jerks. She had questionable left hemiparesis and difficulty in toe clearing especially on the left. She was diagnosed as having spastic cerebral palsy, and was recommended to wear an ankle-foot orthosis. Walking difficulty was worse in the afternoon. She assumed abnormal left shoulder hyperabduction and elbow semiflexion on walking. She learned to write and play the piano at age 3. Slowness in writing and not being able to play the piano well made her quite fretful at class. On examination at age 4, she had hemiparetic posture with fisting on the left. DTRs were slightly increased in the legs with downgoing toes. She had spastic, but wide-based dragging gait. Trihexyphenidyl 3 mg/day was tested with good but incomplete response. When L-dopa/carbidopa 50 mg/day was started, she became very hyperactive and choreic. Slow-release form of L-dopa/carbidopa 25 mg/day gave her smooth start, and was gradually increased to 100 mg/day. She is functioning normally and is much happier during piano lessons.