REVIEW

Recognizing Atypical Dopa-Responsive Dystonia and Its Mimics

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Abstract

Purpose of Review

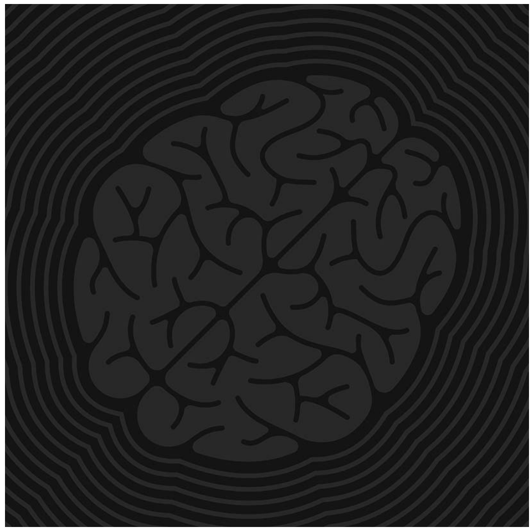
Dopa-responsive dystonia (DRD) encompasses a group of phenotypically and genetically heterogeneous neurochemical disorders. Classic GTP cyclohydrolase 1 (*GCH-1*)–associated DRD consists of early-onset lower limb asymmetrical dystonia, with sleep benefit, diurnal variation, and excellent and sustained response to low L-dopa doses.

Recent Findings

Unlike the classic phenotype, *GCH-1*–associated DRD may include features inconsistent with the original phenotype. We describe a *GCH-1*–associated late-onset DRD case with a family history of parkinsonism and cervical dystonia whose response to levodopa was poor and complicated with dyskinesia, blepharospasm, and severe nonmotor symptoms. We use this case as a springboard to review the spectrum of atypical DRD, DRD-plus, and DRD mimics.

Summary

GCH-1–related dystonia may exhibit wide intrafamilial phenotypic variability, no diurnal fluctuation, poor response to L-dopa, and such complications as dyskinesia, epilepsy, sleep disorders, autonomic dysfunction, oculogyric crisis, myoclonus, or tics. More recently, rare *GCH-1* variants have been found to be associated with Parkinson disease. Clinicians should be aware of atypical DRD, DRD-plus, and DRD mimics.



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Video

In 1976, Segawa described "hereditary progressive dystonia with marked diurnal fluctuation,"[1] followed in 1988 by Nygaard and Duvoisin report of a robust response to L-dopa, for the first time coining the label, dopa-responsive dystonia (DRD).[2] DRD is most commonly of childhood or adolescent onset, inherited in an autosomal dominant manner with incomplete penetrance.[3,4] Less frequently, there is later onset and autosomal recessive inheritance.[2,5] Likely underdiagnosed,[3] its prevalence is estimated to be about 0.5 cases per million in the general population, representing 5%–10% of primary dystonias in childhood and adolescence.[6] Symptoms emerge as a consequence of a nigrostriatal dopamine deficiency due to enzymatic abnormalities in the catecholaminergic biosynthesis pathway.[7] The most frequent enzymatic defect is determined by more than 250 pathologic variants in the GTP cyclohydrolase 1 (*GCH-1*) gene at locus 14q 22.1–22.2, which encodes the GCH-1 protein.[8] This protein catalyzes the synthesis of tetrahydrobiopterin (BH_4), a tyrosine hydroxylase (TH)

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cofactor, whose deficiency limits the synthesis of dopamine, particularly in the ventral portion of the striatum, rich in D1 receptors.[1,4] Furthermore, as BH_4 is the cofactor for tryptophan hydroxylase and phenylalanine hydroxylase, serotonin and phenylalanine production is also compromised[9] (Figure 1).

In its prototypical presentation, DRD presents with lower limb action dystonia, expressed as a unilateral or asymmetric equinovarus posture during (and ultimately affecting) walking, accompanied by marked diurnal fluctuation (i.e., sleep benefit and evening worsening). Besides GCH-1 deficiency, mutations in other genes may manifest this phenotype with some clinical variability according to the affected enzyme.[2,10] Such is the case of sepiapterin reductase (SR) and TH,[2] collectively classified within the clinically heterogeneous group of disorders defined as DRD-plus.[7,11]

We present here an atypical presentation of GCH-1–related DRD using the opportunity to review the relevant literature.

Case

This 34-year-old woman with no perinatal history nor exposure to dopamine receptor–blocking drugs or other medications manifested a slowly progressive equinovarus position of the right foot when walking, beginning at the age of 20 years. There was no diurnal fluctuation. She endorsed a sensation of rigidity and pain in her lower limbs when walking, greater on the right, and experienced partial relief when at rest. The lateral part of her shoes was excessively worn and could not use high-heel shoes.

Her father (II-3) developed Parkinson disease (PD) at age 58 years, with REM sleep behavior disorder and constipation as prodromal manifestations. He was treated with L-dopa at low doses (300 mg/d) with sustained response and no complications after 5 years of treatment. Her niece (IV-2) was diagnosed with DRD at age 13 years, caused by the variant *GCH-1* NM_000161.3(GCH1):c.344-1G>C, which is classified as pathogenic. This variant is located in a canonical splicing site, and it has previously been reported in clinvar (#RCV000540760.2) as causing a condition similar to that of our report. She exhibited a typical walking-induced foot dystonia with an optimal response to L-dopa. Finally, her paternal aunt (II-2) had adult-onset cervical dystonia, treated with botulinum toxin chemodenervation, apparently never treated with levodopa (Figure 2).

Examination at the age of 28 years showed bilateral foot dystonia. At that time, genetic evaluation confirmed the same mutation documented in her niece in a heterozygous form. Treatment with L-dopa 100 mg daily, with gradual adjustment up to 300 mg/d, modestly improved her walking, with substantial residual dystonia in the right foot.

Between the ages of 30 and 34 years, she was diagnosed with blepharospasm, insomnia, and early arousals with diurnal hypersomnia, anxiety, and depression. There was increasing bilateral lower limb pain along with persistent right-foot inversion when walking and new onset of jerky postural tremor of the upper limbs (Video 1). Motor symptoms had a partial response to increasing doses of L-dopa/benserazide, reaching a maximum dose of 600 mg/d divided into 3 doses. Her blepharospasm disappeared with L-dopa, but dyskinesia expressed as chorea of the upper limbs and right torticollis prompted a reduction in the dose to 400 mg/d divided into 4 doses.

Regarding her nonmotor symptoms, there was persistent insomnia, refractory to L-dopa and nonpharmacologic treatments. A polysomnography was performed, which showed a long sleep latency (45 minutes) and long REM latency time (175 minutes), with nocturnal awakenings (48 minutes), poor sleep efficiency, reduced slow-wave sleep (8.8% of the total sleep time) and REM sleep (14.8% of the total sleep time), high index of microarousals, and no respiratory events. Sleep hygiene recommendations and the sequential use of bedtime melatonin 6 mg, mirtazapine 15 mg, and trazodone 100 mg yielded no benefits. Symptomatic response was only achieved with zolpidem CR 10 mg at bedtime. At the time of this report, she was also on treatment with duloxetine 60 mg once daily for anxiety and depression, achieving only partial response. Collectively, her phenotype was considered atypical for DRD.

Considering the low penetrance of the GCH-1 variant found and the atypical features, we also tested ceruloplasmin levels and thyroid, liver, and renal function, which were normal. Her brain MRI was also normal.

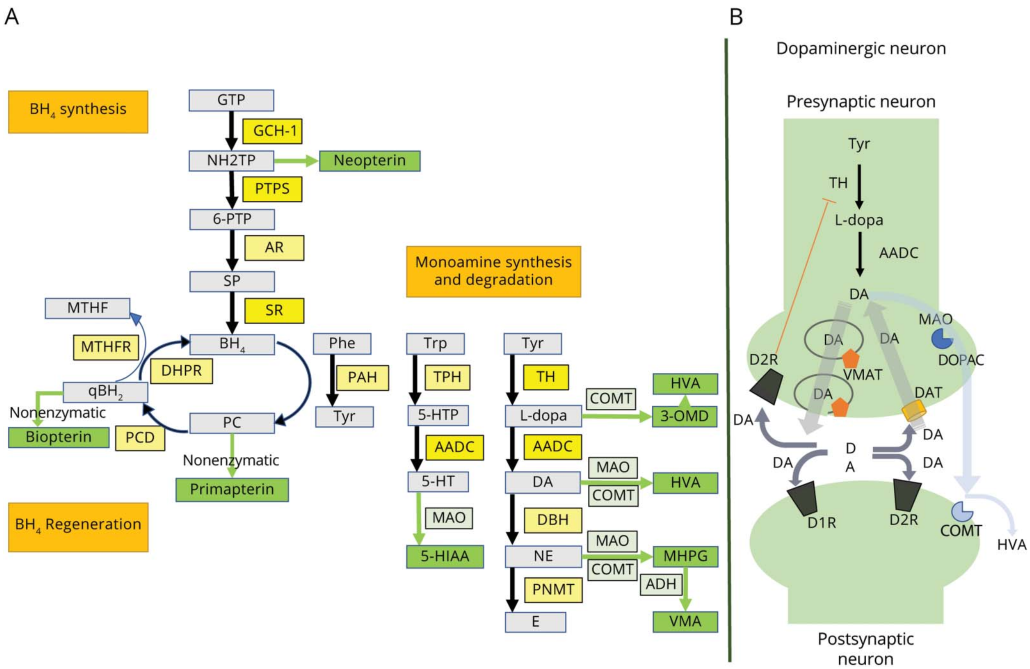
Dopa-Responsive Dystonia

Because of the conservation of a normal allele, autosomal dominant DRD (DYT5a) is associated with a less severe enzymatic defect than the autosomal recessive variants.[2,7,10] Its penetrance is higher in women (87%) compared with men (35%),[12] and accordingly, its incidence is 2.5–4 times higher in women.[6,13] The age at presentation shows a bimodal peak with sex differences. Onset typically occurs in childhood or adolescence, with a mean age of 11.6 years,[2,4,14] and a younger onset in females. The second onset peak is in adulthood, between the third and sixth decades.[2] This last type is more frequent in males,[15] with parkinsonism or tremor as the main or only clinical manifestation.[12,15,16] Some cases manifest both dystonia and parkinsonism.[17]

One-third of patients with DRD have a family history of PD.[18] It has been hypothesized that mutations in *GCH-1* represent a risk factor for PD, even in the absence of a family history of DRD.[17-19] Exome sequencing studies showed a 7-fold greater risk of PD development.[19] Whether parkinsonian or dystonic, the phenotype may depend on epigenetic and environmental factors.[18,19]

In young-onset cases, dystonia is initially markedly asymmetric, involving 1 lower or upper limb, and progressing in half of those

Figure 1 Biosynthetic Pathways



Biosynthesis and regeneration of biopterin and monoamines (A). Dopaminergic synapse (B). 3-OMD = 3-ortho-methyldopa; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HT = serotonin; 5-HTP = 5-hydroxytryptophan; 6-PTP = 6-pyruvoyltetrahydropterin; AADC = aromatic L-amino acid decarboxylase; ADH = alcohol dehydrogenase; AR = aldose reductase; BH_4 = tetrahydrobiopterin; COMT = catechol-O-methyltransferase; D1R = dopamine receptor type 1; D2R = dopamine receptor type 2; DA = dopamine; DAT = dopamine active transporter; DBH = dopamine beta-hydroxylase; DHPR = dihydropteridine reductase; DOPAC = 3,4-dihydroxyphenylacetic acid; E = epinephrine; GCH-1 = GTP cyclohydrolase 1; GTP = guanosine triphosphate; HVA = homovanillic acid; L-dopa = levodopa; MAO = monoamine oxidase; MHPG = 3-methoxy-4-hydroxyphenylglycol; MTHF = methyltetrahydrofolate; MTHFR = methylene tetrahydrofolate reductase; NE = norepinephrine; NH2TP = D-erythro-7,8-dihydroneopterin triphosphate; PAH = phenylalanine hydroxylase; PC = pterin-4-alpha-carbinolamine; PCD = pterin-4-alpha-carbinolamine dehydratase; Phe = phenylalanine; PNMT = phenylethanolamine N-methyltransferase; PTPS = pyruvoyl-tetrahydropterin synthase; qBH_2 = quinonoid-dihydrobiopterin; SP = sepiapterin; SR = sepiapterin reductase; TH = tyrosine hydroxylase; TPH = tryptophan hydroxylase; Trp = tryptophan; Tyr = tyrosine; VMA = vanillylmandelic acid; VMAT = vesicular monoamine transporter.

without treatment, to a segmental or generalized dystonia.[1,3] Physical activity exacerbates clinical symptoms,[2,7] and diurnal fluctuation is a feature in 80%–94% of the cases[4,8,15] but decreases with age.[2]

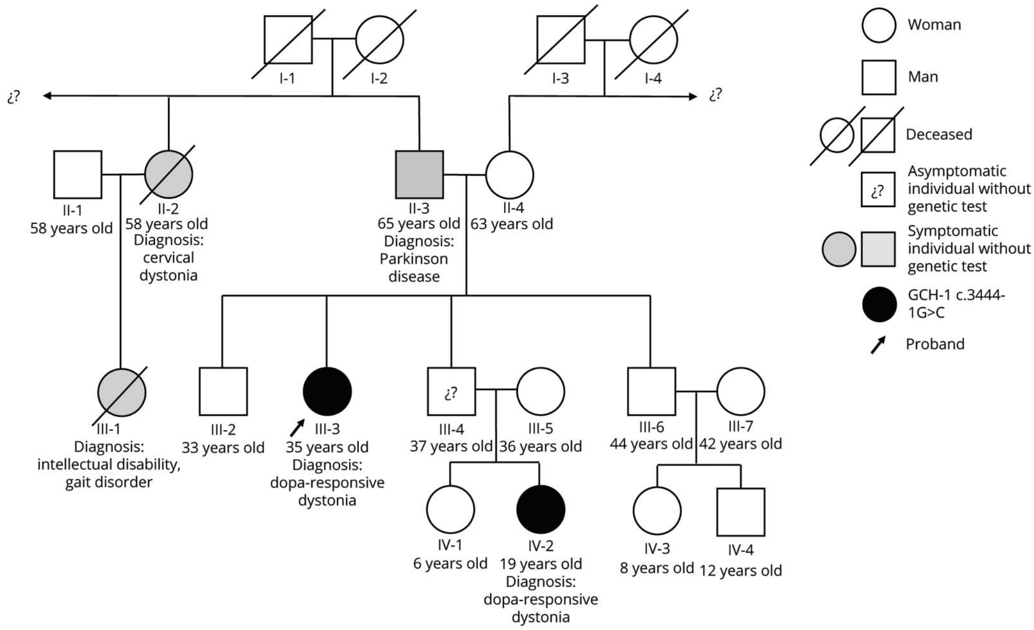
On neurologic examination, muscle stretch reflexes may be enhanced, but no other pyramidal signs should be present, as neither should cerebellar, sensory, or cognitive signs.[8] There have been reports of cognitive impairment in patients with young-onset DRD without treatment.[20] Cardiologic and autonomic systems are generally spared.[21,22] In parkinsonian phenotypes, patients can manifest postural tremor[23] and retropulsion on the pull test.[1] Myoclonus-dystonia, spastic paraplegia, and cerebral palsy have been reported as atypical phenotypes.[4,16] Mood disorders, generalized anxiety, agoraphobia, and obsessive-compulsive disorder can be present because of associated serotonin pathway dysfunction.[21,23] Major depression has been reported in more than 20% of cases and depressive symptoms in ~50%, negatively affecting the quality of life. Psychiatric symptoms can appear in the premotor phase.[21]

Although infrequent in children, sleep disorders are present in about 55% of adults with DRD. Other than sleep benefit in motor symptoms, daytime sleepiness, nonrestorative sleep, and insomnia are common.[24] Polysomnographic studies have revealed periodic limb movements, REM sleep behavior disorder, and increased latency to REM sleep. Abnormal movements during sleep have been reported after the onset of levodopa.[25]

Classic DRD patients show a marked and sustained response to L-dopa, with doses lower than 300 mg per day, in most cases.[7,8] Complications such as motor fluctuations, end-of-dose wearing off, and L-dopa–induced dyskinesia are atypical.[25] Some authors report the absence of motor fluctuations but chronic dyskinesia.[23] However, a systematic review documented a rate of L-dopa–induced dyskinesia in *GCH-1*–associated DRD of 13.3% in autosomal recessive cases and 5.4% in autosomal dominant cases.[26] Dyskinesia has been considered peak-dose and responds to a dose reduction. Anticholinergic agents can attenuate the dystonia and be relied on to reduce the need for L-dopa.[27]

Structural neuroimaging studies are normal. PET and SPECT with presynaptic dopaminergic markers have most frequently shown a normal dopamine uptake in the striatum of patients with DRD and parkinsonism due to pathogenic variants of *GCH-1*,[28] suggesting that dopaminergic nerve terminals are not impaired.[8] However, there are several reports of abnormal dopamine transporter (DAT) SPECT, implying nigrostriatal denervation in *GCH-1* carriers

Figure 2 Genogram in Case Study



Only the 2 youngest members of the family have had genetic confirmation of a *GCH-1* c.3444-1G>C mutation. GCH-1 = GTP cyclohydrolase 1.

manifesting adult-onset parkinsonism or, more rarely, in asymptomatic adult cases.[29,30] The progression of nigrostriatal degeneration was demonstrated in a woman carrying a *GCH-1* pathogenic variant, manifesting parkinsonism at age 47 years. Serial FP-CIT PET scans showed a normal initial pattern followed by a continuous decline of the putaminal binding ratio at 2, 8, and 11 years from disease onset.[31,32] Therefore, an abnormal DAT scan does not rule out *GCH-1* cases, and these patients are at high risk of developing a neurodegenerative parkinsonism.

In clinical practice, these imaging techniques aid in the distinction of DRD-like diseases, such as homozygous carriers of pathologic variants in the *Parkin* gene (*PARK2*) or spinocerebellar ataxia types 2 and 3 (SCA2 and SCA3).[2,33]

Pathologic studies in carriers of *GCH-1* variants developing DRD have shown decreased levels of tetrahydrobiopterin and neopterin, with preserved nigrostriatal dopaminergic terminals. Absence of nigral cell degeneration was shown in the autopsy of a patient with DRD with more than 80 years of disease progression.[34] Although we are not aware of pathologic reports of cases of *GCH-1*–related adult-onset parkinsonism, Lewy body pathology and neuronal loss in the nigral cells and locus coeruleus was reported in a case (heterozygous for c.276delC) who presented with juvenile-onset DRD and parkinsonism complicated by early development of disabling levodopa-induced dyskinesia and death at 39 years.[35,36] This is consistent with the recent discovery that rare *GCH-1* variants, previously reported as pathogenic of DRD, are associated with PD[19] with a phenotype consistent of younger age at onset and milder motor symptoms but more autonomic dysfunction.[37]

When the clinical manifestations are prototypical of classic DRD, the diagnosis can be straightforward. However, in cases like ours with atypical manifestations (older age at onset, absence of diurnal fluctuation, partial response to L-dopa, peak-dose dyskinesia, sleep, and neuropsychiatric difficulties), a broader spectrum of differential diagnoses needs to be considered.

DRD-Plus

DRD-plus is a term used in reference to young-onset cases in which L-dopa–responsive dystonia includes motor or nonmotor symptoms beyond those expected for classic DRD.[5,7] Atypical features include psychomotor retardation, progressive encephalopathy, microcephaly, hypotonia, spasticity, eating disorders, epilepsy, sleep disorders, hyperthermia, ptosis, autonomic dysfunction, ataxia, oculogyric crises, ocular flutter, striatal foot, laryngeal dystonia, myoclonus, tics, different types of focal dystonia, childhood-onset parkinsonism, late-onset parkinsonism, poor response to L-dopa, and L-dopa–induced dyskinesia[7,8,12,23,38] (Table 1). These clinical manifestations are more frequent in monoaminergic disorders with an autosomal recessive inheritance pattern, involving pterin metabolism, enzymatic disorders in monoaminergic synthesis, and transport disorders related to DAT and VMAT (Figure 1).

DRD Mimics

DRD mimics (or "look-alikes") are a group of neurodegenerative and non-neurodegenerative diseases with or without nigrostriatal dopaminergic impairment, presenting as dystonia and responding to dopaminergic drugs, thus mimicking

Table 1 Genetically Determined Monoaminergic Disorders

	Pterin metabolism			Monoaminergic synthesis		Transportopathies	
	AR GCH-1	PTPS	SR	TH	AADC	DAT	VMAT2
Clinical features							
Age at onset	Infancy or childhood	Infancy or childhood	<6 y	<5 y	Infancy or childhood	Childhood	Childhood
Phenotype	DRD; DRD-plus	DRD-plus	DRD	DRD-plus	DRD-plus	DRD-plus; OF	DRD-plus
Diurnal fluctuation	Yes	Yes	Yes	Yes	Yes	Absent	Absent
L-Dopa response	Good	Partial	Good	Partial	Partial	Partial	Absent
Dyskinesias	Possible	No	Possible	Frequent	Possible	Frequent	Frequent
Investigations							
NP CSF	Low	High	Normal	Normal	Normal	Normal	Normal
BP CSF	Low	Low	Normal	High	Normal	Normal	Normal
5-HIAA CSF	Low	Low	Normal	Low	Low	Normal	Normal
HVA CSF	Low	Low	Low	Low	Low	High	Normal
3-OMD CSF	Normal	Normal	Normal	Normal	High	Normal	Normal
Serum phenylalanine	Normal/high	High	Normal	Normal	Normal	Normal	Normal
DATscan	Normal	Normal	Normal	Normal	Normal	Altered	Normal
Related gene	*GCH-1*	*PTH*	*SR*	*TH*	*DDC*	*SLC6A3*	*SLC18A2*
Treatment							
Drug of choice	L-Dopa; 5-HT; BH_4	L-Dopa	L-Dopa ± 5-HT	L-Dopa	AD; MAOI; pyridoxine	AD	AD

Abbreviations: 3-OMD = 3-O-methyldopa; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HT = 5-hydroxytryptophan; AADC = aromatic L-amino acid decarboxylase; AD = autosomal dominant; AR = autosomal recessive; BH_4 = tetrahydrobiopterin; BP = biopterin; DA = dopaminergic agonist; DAT = dopamine transporter; DRD = dopa-responsive dystonia; GCH-1 = GTP cyclohydrolase 1; HVA = homovanillic acid; MAOI = monoamine oxidase inhibitor; NP = neopterin; OF = ocular flutter; PTPS = pyruvoyl-tetrahydropterin synthase; SR = sepiapterin reductase; TH = tyrosine hydroxylase; VMAT2 = vesicular monoamine transporter type 2. References.[2,7,9]
Some AR GCH-1 mutation carriers can develop hyperphenylalaninemia in the first 6 months of life, requiring 5-HT and BH_4.

DRD, but in the absence of pathogenic variants known to express DRD and DRD-plus phenotypes.[7] DRD mimics have been reported in cases of DYT1 dystonia,[7,39] SPG11-related hereditary spastic paraparesis,[1,40] spinocerebellar ataxia (SCA) types 2 and 3,[33] juvenile monogenic parkinsonisms, particularly because of *PRKN* mutations (PARK2),[41,42] GLUT1 deficiency, ataxia-telangiectasia,[7] and pallidopyramidal syndrome,[43] among others (Figure 3). Within this category, Wilson disease and Niemann-Pick disease type C are critical to recognize given the availability of specific disease-modifying treatments. Certain clinical features can help distinguish the most common DRD mimics (Table 2).

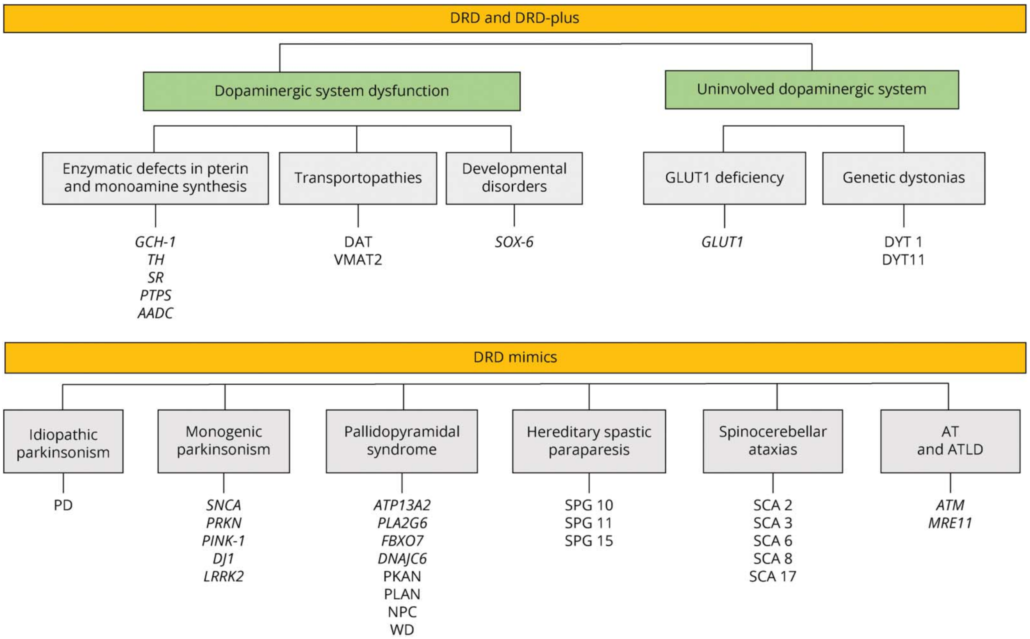
Diagnostic Approach

Basic diagnostic workup depends on the patient's background and symptoms, with L-dopa responsiveness as a major unifying theme. It is generally recommended that every patient with early-onset focal dystonia of unclear nature should have a therapeutic trial with levodopa. Factors in support of the use of levodopa include a family history of dystonia or parkinsonism, atypical age at presentation, dystonia involving the limbs, fluctuations in severity, progression to distant segments, generalization, associated movement disorders, and secondary etiologies. An initial dose of 50 mg levodopa (plus carbidopa or benserazide) 1 to 3 times a day is an acceptable initial dose, which may be slowly increased up to 1000 mg levodopa per day divided into 3 doses for at least 1 month before concluding on its efficacy or lack thereof.[2,44]

In the presence of the classical DRD phenotype, we must study enzymatic deficiencies related to the *GCH-1* gene, explaining about half of the cases, and less frequently TH and SR deficiencies or transport disorders.[3] As L-dopa might alter CSF parameters, it is important to obtain dopamine metabolism measures before its use.[8]

Concentrations of total CSF biopterin, homovanillic acid, 3-O-methyldopa, and total neopterin are reduced in patients with *GCH-1* AD deficiency. When a CSF sample is not available, the evaluation of *GCH-1* activity in mononuclear blood cells stimulated with phytohemagglutinin or fibroblasts stimulated with cytokines can be useful.[8]

Figure 3 Classification and Causes of DRD Syndrome



AADC = aromatic L-amino acid decarboxylase; AT = ataxia-telangiectasia; ATLD = ataxia telangiectasia–like disorders; DAT = dopamine active transporter; DRD = dopa-responsive dystonia; GCH-1 = GTP cyclohydrolase 1; GLUT-1 = glucose transporter type 1; NPC = Niemann-Pick disease type C; PD = Parkinson disease; PKAN = pantothenate kinase–associated neurodegeneration; PLAN = PLA2G6-associated neurodegeneration; PRKN = Parkin gene; PTPS = pyruvoyl-tetrahydropterin synthase; SCA = spinocerebellar ataxia; SOX-6 = SRY-Box 6 transcription factor; SPG = spastic paraparesis; SR = sepiapterin reductase; TH = tyrosine hydroxylase; VMAT2 = vesicular monoamine transporter type 2; WD = Wilson disease.

As a consequence of BH_4 deficiency, a bolus of phenylalanine elicits a high serum phenylalanine/tyrosine ratio 1–2 hours after administration in patients with *GCH-1* and *SR* mutations.[45,46] This test will be normal in cases because of TH deficiency.[47] A high serum level of prolactin can be found in SR and TH deficiencies because of the lack of dopaminergic inhibition; conversely, it can be normal in autosomal dominant *GCH-1* cases.[2,9,48]

In DRD-plus and DRD mimics, PET scans are helpful in recognizing neurodegenerative parkinsonism. MRI can show signal abnormalities in neurodegeneration with brain iron accumulation disorders, SPG11, Wilson disease, and SCAs. From a laboratory standpoint, alpha-fetoprotein, ceruloplasmin levels, acanthocytes, and liver function test should be performed. As we mentioned before, the phenotypic spectrum underlying the term DRD is quite large. Thus, it is desirable to move to a diagnostic approach that incorporates the use of genetic assays such as multigenic panels and/or exome sequencing early in the process, reserving the use of other assays such as structural and functional neuroimaging or biochemical tests to help in the final diagnostic interpretation of a comprehensive genetic evaluation.

Conclusions

DRD encompasses a heterogeneous syndrome of genetic or neurodegenerative diseases, including monoamine and biopterin disorders, with phenotypic pleomorphism compelling their nosologic separation into DRD, DRD-plus, and DRD mimics. GCH-1 deficiency explains about half of the cases exhibiting the classical DRD syndrome originally described by Segawa. Clinicians should be aware of its large clinical variability and the disorders it may mimic. Because of incomplete penetrance, autosomal dominant *GCH-1* mutations may seem to "skip generations" and consequently be falsely considered as autosomal recessive. Remarkably, autosomal dominant *GCH-1* mutations can be associated with sporadic DRD or PD. Moreover, because of variable expressivity, mutation carriers with atypical phenotypes might be considered affected by alternative diseases. Our case study is illustrative of the wide intrafamilial variability of autosomal dominant *GCH-1*–related atypical DRD, including late-onset cervical dystonia and parkinsonism, and highlights the absence of diurnal fluctuation, high threshold for the therapeutic benefit of L-dopa, and L-dopa–induced dyskinesia, all of which were originally considered exclusionary for DRD. Other atypical DRD features include epilepsy, sleep or neuropsychiatric disorders, autonomic dysfunction, oculogyric crisis, myoclonus, or tics, challenging the original *GCH-1* genotype-phenotype alignment.

Acknowledgment

The authors confirm that patient consent was obtained for this work.

Table 2 Comparison Between Adult-Onset DRD and DRD Mimics

	DRD (GCH-1)	DYT-1	*PRKN*-PD	SCA2	SCA3
Frequency	1 per million of persons	17.6–26.1/100.000 persons	2.2% cases of PD 15% young-onset PD	The second most common of SCAs	SCAs 1.5–4.0/100.000 SCA3 the most frequent
Inheritance	AD	AD	AR	AD	AD
Penetrance	Reduced	Reduced	Complete	Full >35 CAG	Full >60 CAG
Age at onset	Childhood-adolescence	Childhood-adolescence	Middle age	Middle age	Middle age
Dystonia distribution reported	Craniocervical Upper limb WC Foot Generalized	Blepharospasm Craniocervical Task specific (limb) Trunk Generalized	Cervical Hand Foot	Orolingual Cervical WC Foot Generalized	Blepharospasm Oromandibular Craniocervical Limbs Generalized
Parkinsonism	Frequent in adult-onset phenotype	Usually absent	Common; asymmetrical > symmetrical	Frequent; symmetrical	Frequent; symmetrical
Tremor	Dystonic; rest (late onset)	Dystonic	Rest > action	Action; rest; perioral	Action; rest; perioral; orthostatic
Motor-neuron signs	Enhanced reflexes	—	Enhanced reflexes	Pyramidal signs ± spasticity; neuropathy	Pyramidal signs ± spasticity; neuropathy
Nonmotor symptoms	Psychiatric; sleep; pain	Psychiatric	Psychiatric; impulse control disorder; sleep; hyposmia	Psychiatric; sleep; cognitive; hyposmia; autonomic	Psychiatric; sleep; cognitive; hyposmia; autonomic; pain; fatigue
Response to L-dopa	Sustained, low doses	No	Sustained, low doses	Levodopa-responsive parkinsonism Dystonia may respond	Good response but not sustained in some cases Dystonia may respond
LDID	Rare	Absent	Frequent	Rare	Rare
Sleep benefit	Majority of the cases	No	About half of the cases	No	Rare
Progression	Stationary with treatment	Generalization	Slow progression	Slow progression	Slow progression
DBS	Good response (STN-DBS)	Good response (GPi-DBS)	Good response (STN- or GPi-DBS)	Good response (ViM, GPi- and STN-DBS)	Good response (GPi-DBS)
Brain MRI	Normal	Normal	Normal	Pontocerebellar atrophy	Pontocerebellar atrophy
PET metabolic activity	Normal	↑ Striatum, cerebellum, and SMA	↓ Striatum	↓ Cerebellum, pons, parahippocampal gyrus, and frontal cortex	↓ Cerebellum, parahippocampal gyrus, and lentiform nucleus
Transcranial sonography	SN hyperechogenicity	Normal	SN hyperechogenicity	SN hyperechogenicity	SN and striatal hyperechogenicity

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DBS = deep brain stimulation; DRD = dopa-responsive dystonia; GCH-1 = GTP cyclohydrolase 1; GPi = internal globus pallidus; LDID = L-dopa–induced dyskinesias; PD = Parkinson disease; PRKN = Parkin gene; SCA = spinocerebellar ataxia; SMA = supplementary motor area; SN = substantia nigra; STN = subthalamic nucleus; WC = writer's cramp.

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TAKE-HOME POINTS

- → Age at onset of *GCH-1* mutation carriers presents a bimodal peak, with "classic" DRD often manifesting in childhood and atypical DRD and parkinsonism in adulthood.
- → Atypical manifestations of *GCH-1*–DRD include absence of diurnal fluctuation, poor response to L-dopa, and such complications as dyskinesia, epilepsy, sleep disorders, autonomic dysfunction, oculogyric crisis, myoclonus, or tics, incongruent with the original *GCH-1* genotype-phenotype observations.
- → Autosomal recessive monoaminergic disorders involving pterin metabolism, enzymatic disorders in monoaminergic synthesis, and transport disorders of DAT and VMAT may express a DRD phenotype with atypical neurologic manifestations.

Appendix Authors

Name	Location	Contribution
Philippe A. Salles, MD	CETRAM, Santiago, Chile	Design and conceptualized the study and drafted the manuscript for intellectual content
Mérida Terán-Jimenez, MD	CETRAM, Santiago, Chile	Design and conceptualized the study and drafted the manuscript for intellectual content
Alvaro Vidal-Santoro, MD	Fuérza Aérea de Chile Hospital, Santiago, Chile	Assisted in the drafting of the manuscript
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