DOPA-RESPONSIVE DYSTONIA COMPLEX: CLINICAL CHARACTERISTICS, DIAGNOSIS, MANAGEMENT

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Abstract

Dopa – responsive dystonia (DRD) is a clinically and genetically heterogeneous condition that is caused by the deficiency of enzymes involved in dopamine biosynthesis. Autosomal dominant mutations in GTP cyclohydrolase 1 account for most cases. DRD typically manifests in childhood or adolescence with dystonia of the lower limb, which might spread gradually during the following decades to other body parts. Symptoms exhibit a characteristic diurnal fluctuation and show a remarkable response to low doses of levodopa, rendering DRD a treatable disorder. Atypical cases have also been described with more severe phenotypes linked to various genotypes. Diagnosis is eventually based on appropriate targeted or non-targeted genetic analysis. Long delays in diagnosis are not a rare phenomenon, thus, a levodopa trial is always advisable in suspicious cases. Here, we present the DRD complex according to the new dystonia classification system of 2013.

Introduction

Dopa – responsive dystonia (DRD) is a genetically heterogeneous, treatable movement disorder, which is caused by the deficiency of enzymes involved in dopamine biosynthesis. As such, it is considered a biochemical, rather than a neurodegenerative movement disorder [1]. While dystonia is its most typical clinical characteristic, DRD can present with additional motor and non-motor symptoms.

The DRD prevalence is estimated at 0.5-1/1,000,000 [2]. The generic term of DRD was introduced by Nygaard et al. in 1988, in order to distinguish the condition from other forms of childhood- or adolescence-onset dystonia or juvenile Parkinson's disease (JPD) [3]. However, case reports of the most prevalent subtype [4], mediated by the inheritable by the autosomal dominant pattern, deficiency of the enzyme GTP cyclohydrolase 1 (GCH1), also known as Segawa disease, were described more than a decade earlier [5]. In 1998, Lee et al. suggested the term "DRD-plus" to describe atypical DRD cases with additional symptoms that did not respond well to dopamine substitution[6].This term, although frequently encountered in the literature of movement disorders [7], was abandoned after the introduction of the recent 2013 dystonia classification system, which integrates two axes: the clinical (axis I) and the subjacent etiology (axis II) [8].

Here, we present DRD based on the new dystonia classification system [8], with relevant terms highlighted in bold throughout the text.

Clinical characteristics (Axis I)

1. Age at onset

DRD typically appears in **childhood or adolescence** [1], although many atypical cases have been reported, with symptoms starting from early infancy [9] to late adulthood [10] (Table 1). Women usually present symptoms at a younger age [11]. DRD is three times more common in women compared to men [9], partly due to the fact that GCH-1 gene mutations' prevalence and penetrance are higher among females [1]. Fever has been recently described as a triggering factor preceding symptoms onset [2].

2. Body distribution

The classic initial presentation of DRD is limb dystonia, most commonly of the lower extremity (**focal dystonia**) [1]. It usually develops as an **action-specific** dystonia of the lower limb, leading to equinovarus foot posturing that often results in walking impairment [1]. In case of upper limb dystonia, focal hand dystonia is the most common manifestation [12]. Within the next two decades, dystonia may spread to adjacent body parts and evolve to **segmen-**

Table 1. Age of onset in DRD

Author, date	Sample characteristics	Sample size	Age		Notes
			($\bar{x}$ ± SD) (y)	(range)	
Trender-Gerhard, 2009 [12]	DRD & GCH-I deficiency	34	8.5	0-48y	Adult onset in 4 patients ($\bar{x}$ =37y).
Tadic, 2012 [11]	DRD & GCH-I deficiency	352	11.6±13.4	–	Homozygous cases excluded.
Tadic, 2012 [11]	DRD & GCH-I deficiency	28	9.4±7.7	–	–
Segawa, 2013 [13]	DRD & GCH-I deficiency	28	6.9±2.9	16mo-13y	A 58y old excluded.
Dobricic, 2017 [14]	DRD	47	18.7±13.6	1-50y	GCH-1 mutations in 11/47 (12.0±9.77).
Ahn, 2019 [15]	DRD & GCH-I deficiency	39	9.4	–	–

DRD: Dopa-Responsive Dystonia; GCH-I: GTP Cyclohydrolase I; mo: months; SD: standard deviation; $\bar{x}$: mean; y: years

tal or generalized dystonia, with or without leg involvement [1]. Absence of dystonia, especially in the adult-onset cases, is also possible [13].

3. Temporal pattern

DRD is a **progressive** disorder that reaches a plateau in the fourth decade [13].Dystonic symptoms show remarkable **diurnal** fluctuation (in >80% of cases) [16], which typically involves evening worsening, exacerbation with physical exercise [17], and improvement with sleep or rest [6]. These fluctuations become less frequent with time and disappear by the third decade [1].

4. Associated features

DRD can present as an **isolated dystonia**, although it is usually considered a **combined dystonia** [18]. Mild parkinsonism often accompanies dystonic symptoms in adult-onset cases but only rarely in children [6]. Less often, bradykinesia, rigidity or postural and rest tremor, might dominate the clinical picture [2] or even be the presenting features [19]. Age at disease onset has also been reported to affect the presenting clinical picture. In contrast to childhood-onset patients, who typically develop lower limb dystonia at disease onset, patients with symptoms onset after 15 years of age may present with parkinsonism without dystonia [12, 19]. Moreover, a wide range of pyramidal signs might be noticed, ranging from brisk reflexes in some patients [17, 20] to spastic quadriparesis [17, 19] and abnormal plantar reflexes in others [21].

Many atypical manifestations have been occasionally described including psychomotor retardation, developmental arrest [9, 22, 23], hypotonia [20, 24], mental retardation [17, 19], scoliosis [17, 25], cerebellar dysfunction [17], tics [26, 27], myoclonus [28], or oculogyric crisis [13]. There was an interesting report of a child presenting with waddling gait and proximal weakness, mimicking a myopathy [29].

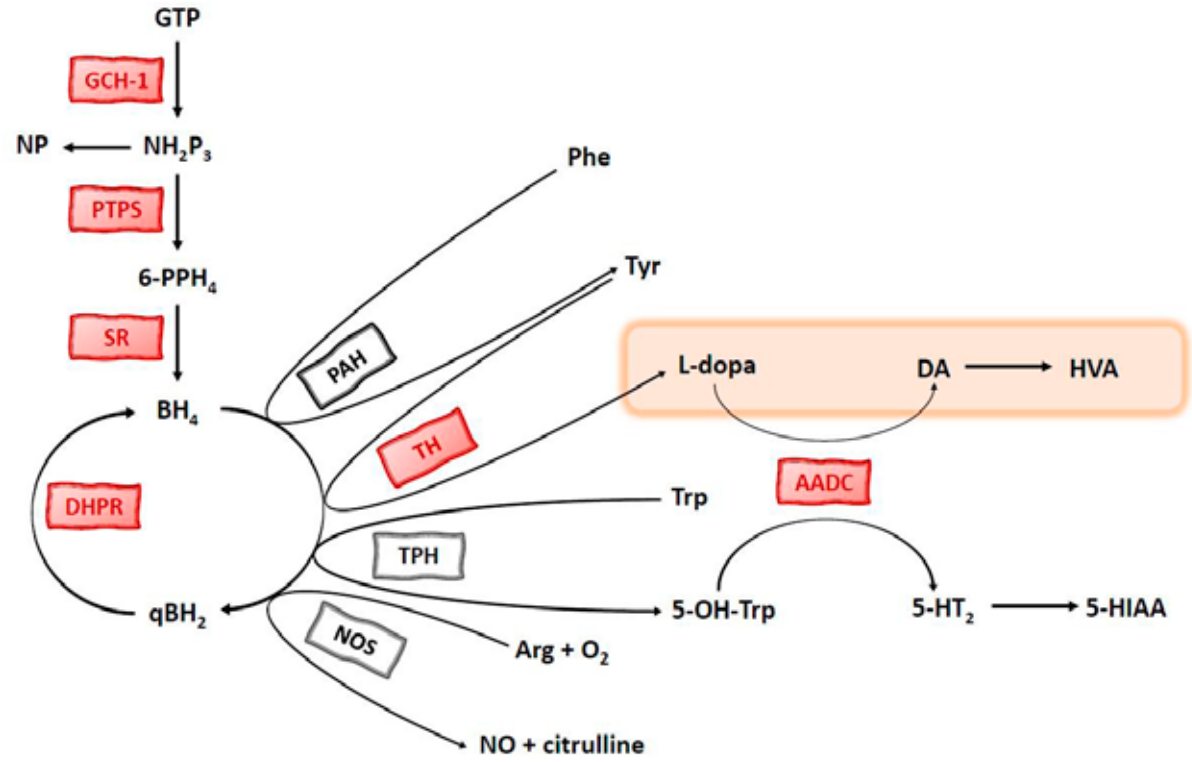
The disorder may also present with a variety of non-motor symptoms that include psychiatric problems, such as mood swings, depression, suicidality [12, 30], anxiety, agoraphobia, obsessive-compulsive disorder [12, 31, 32], as well as fatigue [30], pain [19], constipation, urinary retention, drooling [33], and sleep problems, including somnolence, intense and frightening dreams, difficulty in sleep initiation, or fragmented sleep pattern [31, 32]. Some of them, such as depression, obsessive compulsive disorders and anxiety, are thought to be due to downstream monoaminergic deficiencies [7, 34].

Etiology (Axis II)

1. Nervous system pathology

Symptoms in DRD derive from genetic defects that lead to various degrees of deficiency in enzymes involved in dopamine biosynthesis, in the absence of nigral cell loss [1] (Figure 1). In typical cases, patients present **no evidence of degeneration or structural lesions** in the striatum or substantia nigra. Dopamine levels are lower in the nigrostriatal terminals, but remain normal in the pars compacta of the substantia nigra [1]. However, there have been recent reports showing structural changes in the gray and white matter in the brain of DRD patients, implying alterations of the cortico-subcortical network, al-

Figure 1. Dopamine biosynthesis pathway



AADC: Aromatic L-amino Acid Decarboxylase; **Arg**: arginine; **qBH$_2$**: dihyrdobiopterin; **BH$_4$**: tetrabiopterin; **DA**: dopamine; **DHPR**: dihydropterin reductase; **GCH-1**: GTP cyclohydrolase 1; **GTP**: guanosine 5'-triphosphate; **5-HIAA**: 5-hydroxy-indoleacetic acid; **5-HT$_2$**: serotonin; **HVA**: homovanillic acid; **L-dopa**: levodopa; **NO**: nitric oxide; **NOS**: nitric oxide synthetase; **NP**: neopterin; **PAH**: phenylalanine hydroxylase; **O$_2$**: oxygen; **Phe**: Phenylalanine; **6-PPH$_4$**: 6-pyruvoyl tetrahydropterin; **PTPS**: pyruvoyl-tetrahydropterin synthase; **SR**: sepiapterin reductase; **TH**: tyrosine hydroxylase; **TPH**: tryptophan hydroxylase; **Trp**: tryptofan; **Tyr**: tyrosine.

though it remains unclear if this finding is a primary or secondary effect to dopamine deficiency [35].

Up to now, mutations in six genes have been associated with typical or atypical DRD phenotypes. These genes encode enzymes involved in either tetrabiopterin (BH$_4$) synthesis and recycling, or in neurotransmitter production (Table 2).

2. Inheritance

The enzyme GCH1 is the initial and rate-limiting step in the biosynthesis of BH$_4$, an essential cofactor that mediates the degradation of several amino acids, such as phenylalanine, tyrosine and tryptophane, and the production of monoamine neurotransmitters, like dopamine and serotonin [39].

Mutations of the GCH1 gene are the most common cause of DRD. Both **autosomal dominant and recessive mutations** have been identified. Patients with **autosomal dominant GCH1 mutations** usually maintain some residual enzyme activity and present the benign typical DRD phenotype. In contrary, autosomal **recessive GCH1 mutations** may result in complete absence of functional GCH1 protein and are associated with greater reductions in BH$_4$, hyperphenylalaninemia, and depletion of serotonin and dopamine [6, 7]. Hence, patients with recessive GCH1 mutations may present with a more severe phenotype that may include atypical features depending on the amount of residual enzyme activity [12].

DRD cases due to **autosomally recessive inherited mutations** in tyrosine hydroxylase (TH), sepiapterin reductase (SR) or pyruvoyl-tetrahydropterin synthase (PTPS) genes have also been described. Such cases are much less common and are characterized by an earlier age at symptoms onset and more complex clinical features [2, 4, 40]. PTPS and SR are also involved in the biosynthesis of BH$_4$, while TH constitutes the initial rate-limiting step in the catecholamine biosynthesis pathway [41] (Figure 1). Mutations in dihydropterin reductase (DHPR), an enzyme involved in the regeneration of BH$_4$, have also been linked to DRD [42].

No safe assumptions can be made for a patient's underlying causative mutation based solely on the clinical picture. One specific mutation can be asso-

Table 2. DRD – associated mutations

Gene name	Chromosome location	Enzyme coded	Number of reported mutations [36, 37]
Enzymatic defects of BH_4 synthesis or recycling			
GCH1	14q22.2	GTP cyclohydrolase 1 (GCH1)	192
PTS	11q23.1	Pyruvoyl-tetrahydropterin synthase (PTPS)	34
SPR	2p13.2	Sepiapterin reductase (SR)	19
QDPR	4p15.32	Quinoid dihydropterin reductase (DHPR)	15
Primary neurotransmitter synthesis defects			
TH	11p15.5	Tyrosine hydroxylase (TH)	77
AADC	7p12.2-p12.1	Aromatic L-amino Decarboxylase Decarboxylase*	79

* AACD deficiency results in a more complex phenotype than DRD. It is included here, as patients often present dystonia that respond to dopaminergic agents [38].
BH_4: tetrabiopterin; DRD: Dopamine-Responsive Dystonia; GTP: Guanosine 5'-Triphosphate.

ciated with various degrees of penetrance and residual enzyme function, even in twins [21]. As such, a wide spectrum of phenotypes may be linked to the same genotype, including asymptomatic carriers [6] or even completely different conditions (i.e. GCH1 pathogenic variants in PD patients) [43-45]. In conclusion, it seems that the severity and pattern of DRD phenotype (typical or atypical) is determined mainly by the type and severity of the enzymatic defect and the amount of residual functional protein, rather than the underlying genotype.

Diagnosis

Delays in DRD diagnosis, exceeding 15 years, have been reported in the literature [11]. A common diagnostic pitfall is parkin related-PD especially in cases of adult-onset DRD [46].

DRD chameleons that may warrant a levodopa trial include cases of cerebral palsy (especially among early-onset cases) [9, 22, 23], hereditary spastic paraplegia [21, 47], muscular dystrophy [2], and cervical myelopathy [23]. On the other hand, cases of hereditary spastic paraplegia [48], spinocerebellar ataxia type 3 [49, 50] and ataxia telangiectasia [51] have been reported as DRD mimics as well.

A suggested diagnostic algorithm is depicted in Figure 2 [1, 6, 34] and is analyzed below.

Step 1: Defining the phenotype

In the process of diagnosing DRD, it is helpful to characterize patients' symptoms as suggestive of the typical or atypical DRD phenotype. This distinction can guide further workup to a targeted genetic analysis, as patients with the classic DRD phenotype usually carry an autosomal dominant GCH1 mutation. Those with an atypical phenotype (previously noted as DRD-plus) may harbor genetic defects (usually recessive) on any of the enzymes involved in the dopamine synthesis pathway, which can be missed with the commercially available gene panels.

Step 2: Verifying an excellent levodopa response

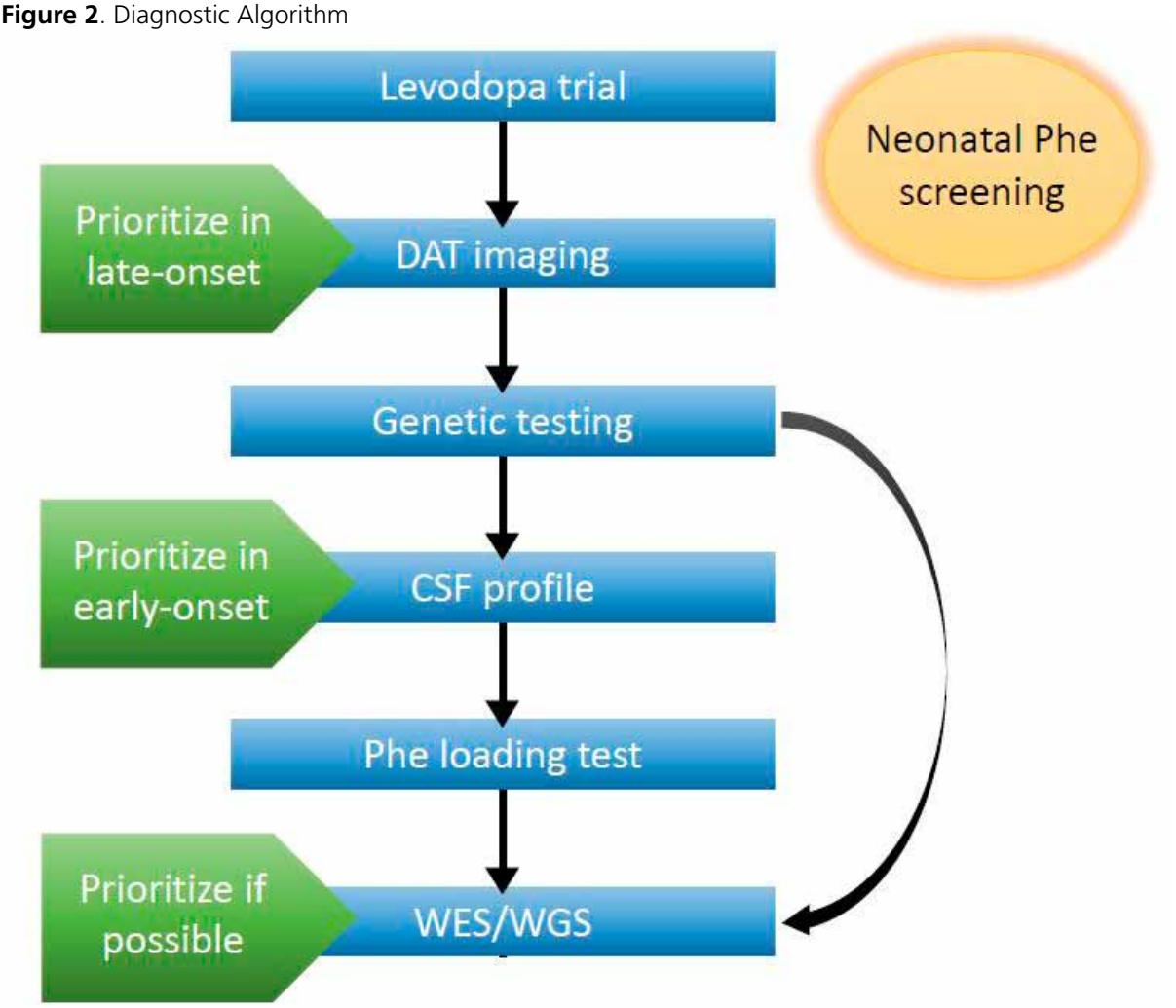
Typical DRD shows a striking and sustained response to small doses of levodopa [6]. Therefore, a levodopa trial should be attempted in all cases of childhood- or adolescence-onset dystonia early in the diagnostic process, even in atypical cases, and despite the absence of lower limb involvement, diurnal fluctuations or a positive family history (see following field of *Treatment*). However, opposing views of DRD over-diagnosis have been expressed, underlying the need for genetic confirmation [52].

Step 3: Ruling out DRD mimics

In patients with the typical DRD phenotype and a good response to levodopa, a targeted genetic analysis should be performed early in the diagnostic process, for the identification of GCH1 mutations.

In patients with atypical DRD symptoms, an inconclusive targeted genetic analysis or suboptimal response to levodopa, further workup is needed. This may include:

Figure 2. Diagnostic Algorithm



CSF: cerebrospinal fluid; **DAT**: Dopamine Transporter; **Phe**: phenylalanine; **WES/WGS**: whole exome/genome sequencing

- ***Imaging with DaTSCAN to rule out nigrostriatal neurodegeneration***

Molecular imaging of the nigrostriatal pathway with DaTSCAN can rule out neurodegenerative disorders of the substantia nigra (SN). A normal result would exclude PD and support a DRD diagnosis [53]. In the rare cases of patients with clinically presumed PD and normal DaTSCAN, often referred to as SWEDD (scans without evidence for dopaminergic deficit) [54], GCH1 mutations are not often encountered [55]. Atypical DRD cases displaying tracer reduction in DaTSCAN have been reported in the literature but are rare [56].

An interesting clinical feature that may be helpful in differentiating DRD from PD is the rarity of levodopa-induced motor complications in DRD patients. In contrast to PD cases, typical DRD patients do not present dyskinesias or fluctuations and do not require levodopa dose titration with disease progression [57]. Delayed levodopa-induced dyskinesias have been occasionally described in up to 20% of DRD patients, however, they are usually mild and quickly subside with levodopa dose reduction, without subsequent motor deterioration [58-60].

- ***Cerebrospinal Fluid (CSF)Studies: Measurement of metabolites***

In DRD patients, determination of neopterin and biopterin levels, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA), and HIV in the CSF, may significantly contribute to the diagnostic process. Not only can they be of merit in ruling out PD, but they can also help in identifying the underlying enzyme deficiency, as levels vary depending on the relevant enzyme position in the biopterin biosynthesis pathway (Table 3).

Low CSF levels of both neopterin (<20 %) and biopterin (Figure 3) is a typical finding of GCH1 deficiency. PD patients also present low levels of these proteins, however, neopterin is expected to

Table 3. CSF and blood neurotransmitters profile [1, 6]

Condition	CSF				Blood	
	Neopterin	Biopterin	HVA	5-HIAA	Phenylalanine	Phenylalanine loading test
GCH1 deficiency	↓	↓	↓	↓	~ *	↑
PTPS deficiency	↑	↓	↓	↓	↑	N/A
SR deficiency	~	↑	↓	↓	~	↑
TH deficiency	~	~	↓	~	~	~
DHPR deficiency	N/A	N/A			↑	N/A
AADC deficiency	~	~	↓	↓	~	~
PD	↓	↓			~	~

*might be high in recessive forms.
CSF: cerebrospinal fluid; **DHPR**: dihydropterin reductase; **GCH1**: GTP cyclohydrolase 1; **N/A**: non applicable; **PD**: Parkinson's Disease; **PTPS**: pyruvoyl-tetrahydropterin synthase; **SR**: sepiapterin reductase; **TH**: tyrosine hydroxylase

be higher than 20% of normal levels, in contrast to GCH1 deficiency [6]. In patients with defects in enzymes that function more distally than GCH1 in the BH_4 biosynthetic pathway, such as SR, salvage pathways are activated that by-pass the enzymatic deficiency and result in normal neopterin and high biopterin levels [7].

Measurement of 5-HIAA and HVA in the CSF can be useful in differentiating DRD from other conditions with similar phenotypes, especially in atypical cases. For example, TH deficiency is characterized by normal neopterin and biopterin levels (distinguishing it from GCH1 and PD), low HVA and normal 5-HIAA levels (Table 3) while AADC deficiency, which is also characterized by normal neopterin and biopterin levels, results in low levels of both HVA and 5-HIAA (Table 3).

• *Blood studies: Phenylalanine Loading Test*

Since BH_4 is a cofactor for phenylalanine hydroxylase (Figure 1), disorders of BH_4 synthesis may present with hyperphenylalaninemia, as a result of impaired phenylalanine metabolism in the liver. Increased blood levels of phenylalanine are a typical finding in the more severe autosomal recessive or compound heterozygous forms of GCH1, PTPS and DHPR deficiencies, thus these conditions are usually diagnosed during neonatal screening and treated timely and accordingly [7, 34]. In autosomal dominant GCH1, TH and SR deficiencies, blood phenylalanine levels at baseline are usually normal [61]. However, hyperphenilalaninemia might arise, if patients are enforced to process a high amount of phenylalanine, as done during the phenylalanine loading test.

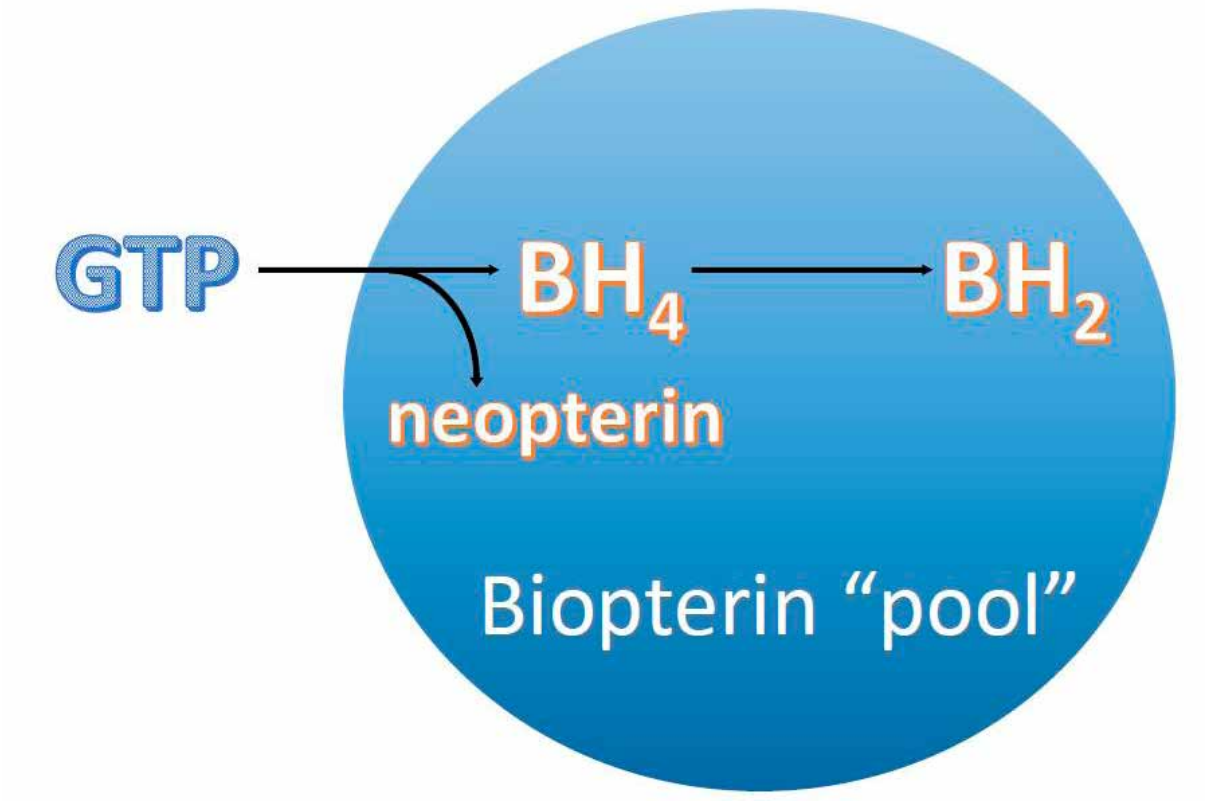
Challenge with Phenylalanine: Adult patients are advised to have a low-protein breakfast approximately two hours before the test. Blood samples are collected for baseline plasma phenylalanine and tyrosine concentration measurements [62]. Then, a loading dose of 100mg/kg of phenylalanine diluted in 100mL of water is administered to the patients [63]. Serial blood tests are performed, and the blood phenylalanine/tyrosine ratio is calculated several times for a period of 4-8 hours [34]. In patients with GCH1 or SR deficiency, an increase in phenylalanine levels will be noted after 1-2 hours, lasting up to 6 hours [34, 63], while the test won't have any effect on those with DRD not related to BH4 synthesis defects such as PD and TH or AADC deficiency [34, 63] (Table 3). In patients with TH or AADC deficiency, the enzymatic defect is located after BH4 production, thus phenylalanine can be normally converted to tyrosine.

The challenge with phenylalanine is particularly useful when lumbar puncture and CSF analysis are not possible [62, 63]. However, false negative and false positive results have been reported [64].

• *Targeted and non-Targeted Genetic Analysis*

Genetic testing plays a fundamental role in DRD diagnosis. GCH1 deficiency constitutes by far the most common form of the disorder. Different types

Figure 3. Biopterin components



BH_2: dihyrdobiopterin; **BH_4**: tetrabiopterin; **GTP**: Guanosine 5'-Triphosphate

of mutations have been reported, including nonsense and missense point mutations, deletions, and duplications, while a significant number of them are sporadic [65]. GCH1 mutations can be detected through commercially available kits [66]. Kits for TH deficiencies are also available in specific clinical settings [1]. However, due to the continuously increasing number of pathogenic mutations identified, this approach leaves room for omissions. Whole exome (WES) or genome sequencing (WGS) is probably the most cost-effective and rewarding type of genetic analysis in the diagnostic process of DRD. However, results should be read with caution, as large deletions, duplications and repeat expansions can be missed. Additionally, special consideration should be given to confirm the relevance of any identified likely pathogenic or novel variants with the condition under investigation [66]. It is worth mentioning that in a cohort of 64 DRD patients, about 17% of them carried no known mutation, suggesting that many causative genetic defects linked to DRD remain to be discovered [4].

Furthermore, patients and their families with a genetic diagnosis of DRD should receive pre- and post-diagnostic genetic counselling. This might not be a straightforward procedure. As penetrance of GCH1 mutations can vary significantly (a 30% penetrance has been reported), some mutations may not necessarily result in a DRD phenotype [67].

Treatment

Regardless of the underlying enzyme deficiency, administration of levodopa plus a peripheral decarboxylase inhibitor, carbidopa or benserazide, is the cornerstone of DRD treatment [1]. DRD patients, especially those with autosomal dominant GCH1 deficiency, show an excellent response to levodopa, with doses significantly lower than those used for PD [68]. Therefore, a levodopa trial is recommended in all childhood- or adolescence-onset dystonia cases, but also in patients with undiagnosed dystonic movement disorders of the adulthood.

Clinicians are advised to "start low and go slow" with levodopa treatment. In children, levodopa is initiated at 1mg/kg/day in divided doses, reaching optimal symptoms' response typically at around 4-5mg/kg/day in the majority of cases [69]. In adults, one should start with 25mg per day and titrate slowly until a satisfactory effect is achieved, or tolerability issues arise [1, 70]. Administration of up to 10mg/kg/day of levodopa in divided doses is recommended for children. Higher doses of levodopa may be required in adults, reaching 600mg/day [71, 72], although

Table 4. Dopa-Responsive Dystonia Treatment [70]

	First-line treatment			Second-line treatment		
	Levodopa	**5-HTP**	**BH_4**	**Anticholinergics**	**DAs**	**MAOIs**
				Trihexyphenidil	**Pramipexole**	**Selegiline**
AD GCH1	+			+		
AR GCH1	+	+	+		+	
PTPS	+	+	+		+	
SR	+	+				
TH	+					+
DHPR	+	+	+		+	
AADC				+	+	+

AD: autosomal dominant; **AR**: autosomal recessive; **BH_4**: tetrabiopterin; **DAs**: Dopamine Agonists; **DHPR**: dihydropterin reductase; **GCH1**: GTP cyclohydrolase 1; **5-HTTP**: 5-hydroxyryptophan; **MAOIs**: monoamine oxidase inhibitor; **PTPS**: pyruvoyl-tetrahydropterin synthase; **SR**: sepiapterin reductase; **TH**: tyrosine hydroxylase

typical cases respond to significantly lower doses (50-300mg). The final dose as well as the time and magnitude of symptoms response are highly individualized and depend on the underlying genetic defect [7]. DRD cases due to enzyme deficiency other than GCH1, with the exception of SR, might need higher levodopa doses, although treatment initiation and titration should always follow the "start low and go slow" principle [70].

As delayed responses have been reported, usually in atypical cases, a levodopa trial should be maintained for three months before considering it unsuccessful [7]. The majority of DRD patients have a long-lasting improvement under a stable levodopa scheme, which is not expected to change over time. However, patients with TH deficiency have been reported to require increasing levodopa doses as the disease progresses [73].

Dyskinesias can rarely appear when initiating treatment with levodopa, especially in atypical cases, and usually signify the need for a lower dose (0.5-1mg/kg daily) [20, 70]. Dyskinesias might also appear later in the disease course, especially in SR and TH deficiency, but usually respond well to levodopa dose reduction or spreading of the doses throughout the day. For persisting dyskinesias, amantadine could be administered at a dose of 4-6mg/kg daily [74].

If motor symptoms are not sufficiently controlled with levodopa, anticholinergic agents, such as trihexyphenidil, can be used either as an add-on treatment or as an alternative monotherapy, in doses ranging from 2-10mg daily [70]. Similarly to levodopa, the initiation dose should be low and the titration slow with regular follow-ups to determine optimal dose.

Dopamine agonists have also been used in selected cases of atypical DRD as second-line treatment. More specifically, in autosomal recessive GCH-1, PTPS and DHPR deficiency, pramipexole in a daily maintenance dose of 0.02-0.04mg/kg was found to be effective [70].

Selegiline, a selective monoamine oxidase (MAO)-B inhibitor has been used as a second-line treatment in TH deficiency cases in daily doses of 0.2-0.4mg/kg, and had a complementary role to levodopa [70].

Residual motor symptoms might persist despite optimal medical therapy. Botulinum toxin can be used to treat focal dystonic phenomena, which are not well controlled with dopaminergic medications [12]. Finally, deep brain stimulation of the globus pallidus internus has been tried in DRD patients with a good response of motor and some non-motor symptoms, such as anxiety and depression, but not cognition [75, 76].

While motor symptoms usually respond perfectly to levodopa, non-motor neuropsychiatric and cognitive symptoms do not. In the more severe autosomal recessive forms of enzyme deficiencies, neuropsychiatric non-motor symptoms usually develop either due to the toxic effect that high phenylalanine levels exert on brain function, or in the context of serotonin deficiency [7]. In such patients, a diet poor in phenylalanine, combined possibly with BH_4 and 5-hydroxytryptofan (5-HTP), a precursor of serotonin, can improve symptoms [7].

Isolated BH_4 therapy fails in restoring neurotransmitter deficiencies, due to poor blood brain barrier permeability and is therefore used in combination with levodopa and 5-HTP. In light of these considerations, a combination treatment of levodopa with 5-HTP has been used as a first-line therapy in cases of SR deficiency and a triple scheme of levodopa, 5-HTP and BH_4, has been successfully tried in patients with

PTS, DHPR or autosomal recessive GCH1 deficiencies [70]. The suggested initial dosage of BH_4 is 1-2mg/kg/day, slowly escalated up to 5-10mg/kg /day. The exact maintenance dose of BH_4 should be adjusted according to serum phenylalanine levels, which have to be maintained at levels lower than 120μmol/L [77].

Treatment with folic acid and pyridoxine should also be considered in certain DRD syndromes. Patients with DHPR deficiency should receive folic acid at doses of 10-20mg per day, as DHPR is required for normal folic acid blood levels maintenance. Pyridoxine should be administered in cases with AADC deficiency,as excess amounts of the enzyme's cofactor can boost residual AADC activity [34].

Conclusion

DRD is a genetic dystonia with very characteristic dystonic symptoms and a good response to treatment. A growing number of underlying causative genetic defects are currently being detected in DRD patients and linked to typical and atypical disease phenotypes. Various degrees of penetrance have been associated with the classic mutations, rendering genetic counseling in carrier families very challenging [78].

Given that DRD is a treatable condition, the diagnosis should always be examined and a low threshold for a levodopa trial up to 600mg sustained for 3 months is recommended as early as possible in all childhood- or adolescence-onset dystonia cases. A timely therapeutic intervention in DRD patients is of paramount importance since treatment can markedly improve patients' quality of life. Nevertheless, even in undiagnosed dystonia cases, reconsideration of the initial diagnosis and a levodopa trial is always of merit, as delayed diagnosis does not exclude a significant improvement following levodopa treatment.

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