

Dopa-responsive Dystonia in Children

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Opinion statement

Treatment of dopa-responsive dystonia is one of the more satisfying experiences in clinical neurology. The response to treatment with levodopa is usually dramatic and complete with no long-term complications. Carbidopa/levodopa is the mainstay in treating dopa-responsive dystonia. There is some experience using anticholinergic agents, but they are more likely to cause side effects and do not treat the underlying biochemical abnormality. Dopa-responsive dystonia caused by guanosine triphosphate cyclohydrolase I deficiency typically presents with dystonia in the lower extremities in the first decade of life. However, the presenting symptoms can vary. Thus, it is this author's recommendation that any child with dystonia receive a trial of carbidopa/levodopa.

Introduction

Dopa-responsive dystonia (DRD) is a condition characterized by the onset of dystonia in early childhood with dramatic and sustained response to treatment with levodopa. Dopa-responsive dystonia was first described by Segawa *et al.* [1] who named the disorder "hereditary progressive dystonia with marked diurnal fluctuation (HPD)". Subsequently, Nygaard *et al.* [2] coined the term *dopa-responsive dystonia* to refer to all dystonias responding to levodopa. The most common form of DRD is an autosomal-dominant condition caused by mutation of the gene for guanosine triphosphate (GTP) cyclohydrolase I [3]. Guanosine triphosphate cyclohydrolase I is the rate-limiting and initial step in the biosynthesis of tetrahydrobiopterin from GTP. Tetrahydrobiopterin is a cofactor for tyrosine hydroxylase, which is the rate-limiting enzyme in the synthesis of dopamine. Tetrahydrobiopterin is also a cofactor for phenylalanine hydroxylase and tryptophan hydroxylase. Autosomal-dominant DRD is characterized by onset in the first decade of life with foot dystonia, which progresses to involvement of other body parts, but typically remains more severe in the lower extremities. The severity increases progressively over the first two decades of life, but plateaus and may actually decrease in the third or fourth decade. There is dramatic and sustained response to low doses of levodopa with relatively few side effects

and no long-term complications, such as those seen in Parkinson disease, of therapy [4•]. Untreated individuals with DRD develop diurnal fluctuations with marked improvement in the morning and worsening in the evening. This is not a constant feature, and it is more apparent in adolescents and young adults than in younger children. Untreated individuals often develop signs of Parkinsonism, including bradykinesia and postural instability. A much less common form of DRD is an autosomal-recessive condition caused by mutation of the tyrosine hydroxylase gene [5]. This condition usually manifests in infancy, with rigidity, abnormal posturing, and decreased spontaneous movements. There can be excessive drooling and ptosis that may reflect deficiency in norepinephrine in addition to dopamine.

Diagnosis of DRD can often be made on clinical grounds. However, there is considerable phenotypic variability, including neonatal hypotonia, dystonia of the upper extremities, myoclonus dystonia, and adult onset of dystonia or Parkinsonism [6•,7,8]. Some individuals have been misdiagnosed with cerebral palsy or hereditary spastic paraparesis; however, there is no spasticity in DRD. Reflexes can be brisk in some individuals, and a "striatal toe" may be misinterpreted as a Babinski sign. Because of the phenotypic variability, it has been recommended that all children with dystonia receive a

trial of levodopa. Other types of dystonia may show some symptomatic benefit from levodopa, but it is rarely as dramatic as the response typically seen in DRD. Complete response to levodopa does not mean that the condition is caused by a GTP cyclohydrolase I mutation, because mutation in the tyrosine hydroxylase or parkin genes can also present like typical DRD [6•]. Genetic testing for GTP cyclohydrolase I mutations is cumbersome, because a large number of mutations have been described, and, thus, the entire gene must be sequenced [9]. Cerebrospinal fluid can be tested for levels of tetrahydrobiopterin, neopterin, and metabolites

of catecholamines and indolamines [10]. This testing is only done by a few laboratories and requires a lumbar puncture. It has been shown that a phenylalanine-loading test can be useful in supporting the diagnosis, and it appears relatively sensitive and specific [11,12••]. Still, clinical response to a trial of levodopa may be the most clinically useful method for diagnosing DRD.

The primary treatment for DRD is levodopa with carbidopa. There may also be good response to anticholinergic medications such as trihexyphenidyl. Dopamine agonists have not been well studied in the treatment of DRD.

Treatment

Pharmacologic treatment

- The goal of drug therapy is complete remission of symptoms, including dystonia and Parkinsonism when present.
- Dyskinesia may occur with initiation of treatment or in older individuals who are treated with relatively higher doses of levodopa. Dyskinesia can be reduced or eliminated by reducing the dose of levodopa.
- Theoretically, treatment with dopamine agonists should be effective, but this has not been studied.

Carbidopa/levodopa

Standard dosage	A starting dose of 1 mg/kg per day of levodopa, gradually increasing until complete benefit or dose-limiting side effects [6•, Class III]. Most individuals respond to 4 to 5 mg/kg per day in divided doses [4•, Class III]. Other authors have suggested doses of 10 mg/kg per day [13, Class III]. If no response to a dose of 600 mg per day, it is highly unlikely that DRD is the correct diagnosis [6•, Class III]. Carbidopa/levodopa should be given as 25/100 mg tablets in children. They can be crushed and dissolved in an ascorbic acid solution or in orange juice and used within 24 hours [14•].
Contraindications	Psychosis, hypotension, and melanoma. These conditions are not associated with DRD and are rare in children.
Main drug interactions	Neuroleptics reduce the benefit.
Main side effects	Somnolence, nausea and vomiting, decreased appetite, dyskinesia, and hallucinations. Nausea and vomiting can be reduced with additional carbidopa, available in 25-mg tablets. Dyskinesia can be reduced or eliminated by reducing the dose [15••].
Special points	If dyskinesia is present with the initiation of treatment, reduce the dose. If inadequate benefit at the lower dose, it can usually be increased again slowly without recurrence of dyskinesia. Motor complications of levodopa therapy that are seen in Parkinson's disease do not occur in DRD.
Cost/cost effectiveness	Highly cost effective if complete control of symptoms is attained. The dose can be reduced to the lowest effective dose to maximize cost effectiveness.

Trihexyphenidyl

Standard dosage	Dosing is not well established in children. Starting dose should be 0.5 mg per day in children younger than 4 years of age and 1 mg per day in older children. The dose should be increased by 1 mg every 3 to 5 days three times daily until benefit or side effects. In DRD, there is benefit from relatively low doses compared with those used to treat other forms of dystonia [16, Class III].
Contraindications	Glaucoma, pyloric or duodenal obstruction, urethral obstruction, achalasia, and toxic megacolon.

- Main drug interactions** May decrease efficacy of antipsychotic medications. Combination with tricyclic antidepressants may increase side effects.
- Main side effects** Dry mouth, blurred vision, constipation, decreased concentration, and hallucinations.
- Special points** Trihexyphenidyl is a second-line treatment, because levodopa reverses the biochemical defect of decreased dopamine synthesis in DRD.
- Cost/cost effectiveness** If benefit occurs before toxicity, the cost effectiveness is excellent.

Physical therapy

- Physical therapy can be helpful if there has been chronic gait impairment or contractures. However, the role for physical therapy is limited, because most patients have complete response to drug therapy

Emerging therapies

- Tetrahydrobiopterin may be a useful treatment [17], but it is not readily available, has not been well studied, and dosing information is not available.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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- This study demonstrates a very high sensitivity and specificity of the phenylalanine loading test with their modifications for making a single measurement of serum phenylalanine after an oral load of phenylalanine.
13. Wang P, Ko Y, Young C, *et al.*: **Hereditary progressive dystonia with marked diurnal fluctuations [Segawa syndrome] in Taiwan.** *Brain Devel* 1994, 16:126–131.
 14. Kurth MC: **Using liquid levodopa in the treatment of Parkinson's disease: a practical guide.** *Drugs Aging* 1997, 10:332–340.
- This manuscript describes a method for dissolving carbidopa/levodopa in an ascorbic acid solution to maintain stability of the compound. It is highly useful, especially when administering the medication to small children. In this author's opinion, orange juice can be used as a substitute for the ascorbic acid solution.

- 15.●● Hwang WJ, Calne DB, Tsui JKC, de la Fuente-Fernandez R: **The long-term response to levodopa in dopa-responsive dystonia.** *Parkinsonism Relat Disord* 2001, 8:1–5.

The authors report on the response to levodopa treatment in DRD patients who had been treated for up to 25 years. Dyskinesias occurred in 20% of patients and improved with dose reduction. There was an inverse relationship between dose and duration of treatment supporting the notion that levodopa requirement decreases with age in DRD.

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