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Clinical Observations

What Is Not in the Name? Dopa-Responsive Dystonia May Respond to More Than L-Dopa

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ABSTRACT

BACKGROUND: Classic L-dopa–responsive dystonia is characterized by the triad of dystonia, diurnal fluctuation of signs, and dramatic response of signs to low-dose L-dopa therapy. Dopa-responsive dystonia succinctly summarizes the relevant clinical features. However, literal application of this label or consideration of dopa-responsive dystonia as a diagnostic end without molecular and/or biochemical definition may contribute to misdiagnosis and incomplete treatment in dopa-responsive conditions that impair synthesis of monoamine neurotransmitters besides dopamine. **PATIENT DESCRIPTION:** We describe and provide video for twin patients with a rare form of dopa-responsive dystonia due to sepiapterin reductase deficiency. As is typical in dopa-responsive dystonia, these patients displayed dramatic improvement with L-dopa/carbidopa therapy. However, treatment was suboptimal until 5-hydroxytryptophan was added to address their serotonergic deficit. **DISCUSSION:** Our report highlights the limitations of the dopa-responsive dystonia label and increases awareness of sepiapterin reductase deficiency and other conditions that may present as dopa-responsive dystonia. We provide a diagnostic and therapeutic approach to guide the clinician in evaluating and treating individuals with dopa-responsive dystonia.

Keywords: dystonia, dopa responsive, DRD, sepiapterin, cerebral palsy

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Introduction

In 1971, Segawa et al. described patients with hereditary progressive dystonia with marked diurnal fluctuation.[1-3] The label dopa-responsive dystonia (DRD) was subsequently coined by Nygaard et al.[4] and has remained a useful descriptive moniker aiding identification of patients with this highly treatable condition. Although most commonly patients with typical DRD possess autosomal dominant mutations in the GTP cyclohydrolase I (*GCH1*) gene, rarely, recessive mutations in *GCH1* or other genes involved in biogenic amine synthesis (tyrosine hydroxylase [*TH*], sepiapterin reductase [*SPR*], 6-pyruvoyl-tetrahydropterin synthase [*PTS*]) and a single individual with autosomal dominant *SPR* mutation have also been associated with the classic phenotype[5,6] (Fig 1). Patients with juvenile Parkinson disease, dopamine transporter deficiency, and other genetic and nongenetic conditions may also derive symptomatic improvement from L-dopa.[7,8]

In spite of increased awareness of DRD among clinicians, there is limited appreciation regarding the lack of specificity of the term and of the potential benefit of nondopaminergic agents in a subset of patients with DRD. The term DRD-plus has been proposed to identify patients who may display more broad signs than classic DRD.[9] Yet, this term remains underutilized, and awareness of the wide phenotypic spectrum and of potential benefit from therapies beyond L-dopa remain under-recognized.

We describe two patients to highlight the hazards of terminating patient evaluation with a diagnosis of DRD and treatment with only L-dopa. Brief description of our patients has been presented elsewhere.[5,10] Here, we provide clinical details and video to increase awareness of clinical features in *SPR* deficiency (SRD) and the utility of combination therapy in this highly treatable condition.

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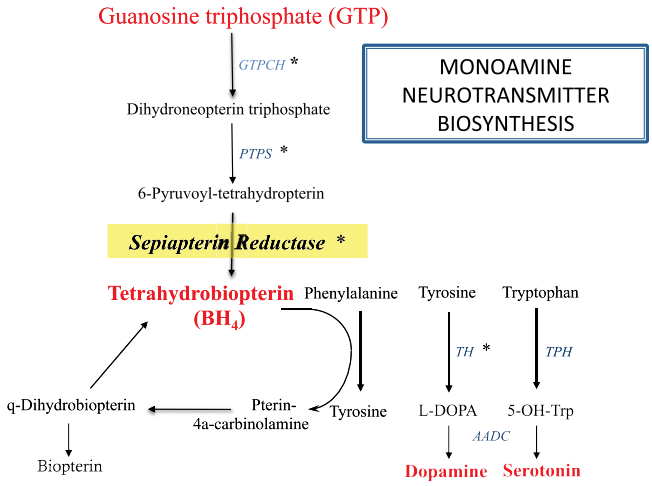

FIGURE 1.
Pathway for the synthesis of the monoamine neurotransmitters dopamine and serotonin. Dopa-responsive dystonia (DRD) has been reported with dysfunction at the steps marked with an asterisk (*). Defects in the tyrosine hydroxylase enzyme lead to DRD by impairing the conversion of tyrosine to L-dopa, the rate-limiting step in the synthesis of dopamine. Treatment with the dopamine precursor, L-dopa, bypasses the block and repletes dopamine. Defects in the enzymes GTPCH, PTPS, and sepiapterin reductase cause DRD by reducing production of tetrahydrobiopterin (BH_4) a cofactor for tyrosine hydroxylase. BH_4 is also a cofactor for tryptophan hydroxylase, and thus dysfunction of these enzymes leads to variable deficiencies of serotonin in addition to dopamine. In these conditions, there may be added therapeutic benefit from the serotonin precursor, 5-HTP, or other strategies to increase serotonin such as serotonin reuptake inhibitors. Abbreviations: 5-HTP, 5-hydroxytryptophan; AADC, aromatic amino acid decarboxylase (*DDC* gene); GTPCH, GTP-cyclohydrolase-1 (*GCH1* gene); PTPS, 6-pyruvoyl-tetrahydropterin synthase (*PTS* gene); TH, tyrosine hydroxylase (*TH* gene); TPH, tryptophan hydroxylase (*TPH1 and TPH2* genes). (The color version of this figure is available in the online edition.)

Patient Descriptions

The patients were the 36-week products of a twin-pregnancy complicated by maternal hypercoagulable state requiring heparin. Birth was unremarkable for the male (Apgar 9/9) and breech for the female (Apgar 6/9). The neonatal period was otherwise noteworthy only for mild jaundice. During infancy, patients were hypotonic, irritable, and had difficulty feeding, frequent emesis, and poor sleep. Developmental milestones were delayed in both with sitting at 14 months (male) and 20 months (female), walking at 20 months (male) and 24 months (female), single words 18 months (male) and 20 months (female), and sentences three years (male) and four years (female). Both were observed to be hypotonic, and the female had limb hypertonicity and tremors. The girl had generalized tonic–clonic seizures mostly with fever and oculogyric episodes that were mistaken for seizures (Fig 2 and Video). Screening metabolic evaluation (chromosomes, plasma amino acids, urine organic acids, and lactate) was unremarkable. The results of brain magnetic resonance imaging and electroencephalograph were normal in the girl, and brain magnetic resonance imaging revealed periventricular leukomalacia in the boy. Based on this finding a diagnosis of cerebral palsy was made in both twins.

FIGURE 2.
Oculogyric crises: the girl is illustrated at age 3 years on no medication. She displays oculogyric crises that are mistaken for seizure. The video related to this figure can be found at 10.1016/j.pediatrneurol.2015.12.016. (The color version of this figure is available in the online edition.)

Both children, though globally delayed, made developmental progress until age 4 years. At age 5 years, the female began to regress with increased difficulty with motor function. After noon, she was unable to speak in full sentences or to hold utensils to feed herself. At times, she was unable to sit. There were paroxysmal episodes of hypokinesia, rigidity, and tremor late in the day (Fig 3 and Video). The onset of dystonia is unclear but was subtly present on home video at 3 years.

DRD was considered because of striking diurnal fluctuation of signs, and a trial of L-dopa was instituted with dramatic improvement of motor and speech function (Fig 4 and Video). The boy was observed to have only subtle fine and gross motor delays and speech articulation problems with minor attention and behavioral difficulties, drooling and daily emesis. Initial evaluation failed to reveal dystonia. On subsequent evaluations and with careful observation prompted by DRD diagnosis in his sister, minimal dystonia was observed, and an L-dopa trial was instituted at age six years. He displayed improvement in gait and drooling, and surprisingly, there was resolution of daily emesis.

The children were diagnosed with DRD and continued to make developmental progress on low-dose L-dopa/carbidopa therapy. They were athletic. The boy performed academically at grade level with mild-to-moderate attention and processing difficulties, and the girl, also with mild-to-moderate attention and processing difficulties, was variably reported at grade level or slightly behind (language 1 year and math 1 to 2 years). The boy displayed intermittent mild drooling, mild hyperactive and impulsive behavior, dysgraphia, and mild hand tremor. The girl had mild anxiety and difficulty maintaining sleep.

At age 11 years, the girl developed progressively worsening symptoms consisting of paroxysmal coughing and dyspnea that made it impossible for her to participate in athletics and at times was associated with severe laryngospasm and cyanosis. Extensive pulmonary, allergy, and gastrointestinal evaluations revealed only mild reflux. Treatment of this did not alleviate her symptoms.