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Case Study

DOPA Responsive Dystonia: A Treatable Condition but Often Missed

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Abstract

Dopa-responsive dystonia (DRD) includes a group of movement disorders disorder that clinically present as limb-onset with diurnal fluctuation dystonia which presents in early life with a good response to levodopa therapy. GTP cyclohydrolase 1 deficiency (Autosomal dominant), otherwise called as Segawa disease, is the commonest syndromic condition that manifests as DRD. Similar features can be seen with other genetic diseases of biosynthesis of dopamine. It starts with involvement of lower limb and it is associated with characteristic diurnal variation. Unfortunately, it's misdiagnosed as cerebral palsy due to early onset, spasticity and selective lower limb preference by many physicians. Due to this, many children with Segawa disease are wrongly treated many times. It's a treatable condition with good response to dopaminergic drugs. Early diagnosis and well dosed levodopa therapy can prevent complications.

Keywords: *Dopa-Responsive Dystonia; Diurnal Variation; Levodopa; Segawa Disease*

Introduction

The disease spectrum of dopa-responsive dystonia (DRD) includes a group of disorders of dopamine synthesis, which shows dramatic improvement with levodopa treatment [1]. The typical progression is early onset limb specific dystonia which starts in lower limb and progress to other limbs and trunk with characteristic diurnal variation. The classic features disappear with sustained and good response to levodopa treatment. Out of the group the most common and studied disorder is Segawa disease (DYT5a). The condition was first brought to limelight by Segawa., *et al*. by the terminology "hereditary progressive basal ganglia disease with marked diurnal fluctuation" but later it was termed as "hereditary progressive dystonia with marked diurnal fluctuation" [2]. It occurs due to autosomal dominant deficiency of GTP cyclohydrolase 1 (GTP-CH-I), which is encoded by GCH1.2 GTP-CH-I helps in the production of an essential cofactor for biosynthesis of monoamine neurotransmitters [3]. Now a days the DRD is not an isolated disease, rather it's a constellation of several diseases. Various enzyme deficiencies can present with similar presenting features in early childhood.

Pathophysiology

Enzyme deficiency	Inheritance	Age of presentation	Other features	Response to levodopa
GTP-CH-I deficiency [4]	AD	Mean 8.5 years, range 0.2–48 years	parkinsonism, Pyramidal features, scoliosis, anxiety, depression, OCD	Well sustained response, Dyskinesia occasional
GTP-CH-I deficiency [5]	AR	Can manifest at <6 months	Spasticity, excessive drooling, oculogyric crises, poor sleep	Well sustained response, but high dose
Tyrosine hydroxylase deficiency [6]	AR	Between a few weeks after birth and 5 years	Progressive hypokinetic–rigid syndrome with dystonia (type A), complex encephalopathy (type B), ptosis, tremor, autonomic disturbance, spasticity, hypotonia, delayed motor developmental milestones, intellectual disability	Good response, frequent dyskinesia
Sepiapterin reductase deficiency [7]	AR	Between birth and 6 years	Oculogyric crises, symptoms of dysautonomia symptoms (tachycardia, hypersalivation), developmental delay, microcephaly or growth retardation, hypotonia, intellectual disability, sleep disorders, parkinsonism, hyperreflexia	Good response, frequent dyskinesia
PTP synthase deficiency [8]	AR	Birth to early childhood	Early childhood seizure, spasticity, mild cognitive deficits	Marked and sustained positive response

Table 1

Presentation

Typical clinical features of DRD are seen in childhood or adolescent age group. The onset of dystonia is associated with mild parkinsonism sometimes. Along with it diurnal fluctuations, and its improved with sleep or rest which is otherwise called sleep benefit, and a well sustained response to low doses of Levodopa are the hallmarks of the disease [9]. A marked and well sustained improvement after L-dopa therapy without significant motor fluctuations or dyskinesias is the landmark feature which helps clinicians to distinguish DRD from other genetic dystonias and early onset parkinsonism. Atypical presentations are also commonly encountered. Variable onset of dystonia at different age ranging from early infancy to late adulthood may be seen. Early infantile DRD mimics cerebral palsy. Many patients are wrongly diagnosed and treated for prolonged period as cerebral palsy [10]. Along with movement disorders, mental retardation, seizures, systemic symptoms, and cerebellar abnormalities have also been reported in rare instances [11,12]. Phenomenal response to L-dopa is the hallmark of DRD. Even treatment is delayed for decades complete resolution of symptoms with incomplete response for action dystonia has been reported, but it's incidence is very rare [13].

Due to wide spectrum of symptoms and signs three syndromic groups are made recently [14] (Table 2).

Syndromic classification [14]	Definition	
DRD	A group of non-neurodegenerative disorders by genetic defects involving nigrostriatal dopaminergic system with manifestations like dystonia and/or parkinsonism, and dramatic response to levodopa without long term motor complications.	DRD Spectrum
DRD-plus	A group of non-neurodegenerative disorders by genetic defects involving nigrostriatal dopaminergic system with dopa-responsiveness plus additional features like infantile onset, developmental delay, psychomotor retardation, seizure, hypotonia, drowsiness, recurrent hyperthermia, ptosis, cerebellar dysfunction, poor responsiveness to levodopa or other dopaminergic drugs that are not seen in DRD	Dopaminergic system, non-neurodegenerative. 1) Enzymatic deficiency in dopamine synthetic pathway 2) Transportopathy DAT deficiency VMAT deficiency 3) Developmental disorder affecting dopamine system: SOX mutation
DRD look-alike	A group of 1) neurodegenerative or non-neurodegenerative disorders without involving the nigrostriatal dopaminergic system or 2) neurodegenerative disorders with involving nigrostriatal dopaminergic system, that could present with dystonia responsive to dopaminergic drugs	dopaminergic system, neurodegenerative 1) Juvenile Parkinson's disease 2) Pallidopyramidal syndrome 3) Spinocerebellar ataxia type III. Non-neurodegenerative disorder DYT 1 GLUT deficiency syndrome Myoclonus-dystonia Neurodegenerative disorder Ataxia telangiectasia Undetermined disorder Levodopa-responsive camptocormia

Table 2: *DRD differential DD.*

Diagnosis

Levodopa trial [15]: The first step and cornerstone in the diagnosis of DRD is to establish the response to levodopa which is otherwise called levodopa trial. The levodopa is given in combination with a peripheral decarboxylase inhibitor, to increase its efficacy. The trial separates DRD from other primary dystonias, because they don't naturally respond to levodopa, rather they respond well to dopamine depletors. For children aged < 6 years, 1 - 10 mg/kg levodopa daily, given in multiple doses, along with a peripheral decarboxylase inhibitor in combination. For patients aged > 6 years, a trial of 12.5 mg carbidopa and 50 mg levodopa one to three times daily with meals for 1 week, increasing to 25 mg carbidopa and 50 mg levodopa three times daily for 1 week, followed by 50 mg carbidopa and 200 mg levodopa three times daily. If no improvement was is seen after 1 month, the levodopa trial should be marked as a failure. Children who present with episodic oculogyric crisis, general dystonia, early onset parkinsonism and encephalopathy, trial of 0.5 - 10 mg/kg levodopa daily, should be administered in multiple divided doses with a combination of a peripheral decarboxylase inhibitor for at least 2 - 3 months. If it responds well the trial will be considered positive.

Imaging: Use of advanced imaging studies like PET and SPECT studies are limited in DRD, but they might help in differentiation between DRD and juvenile PD. In juvenile PD, fluorodopa uptake and dopamine transporter density are decreased, whereas abnormalities in these parameters are minimal in DRD [16].

Cerebrospinal fluid and blood analysis: CSF analysis helps to assess the levels of neurotransmitters and metabolites (such as homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5 HAA), neopterin and biopterin) in cerebrospinal fluid (CSF), and phenylalanine in blood. In the phenotype with GTP-CH-I deficiency all the values of metabolites are low whereas the blood phenylalanine level is normal [17].

Others: Phenylalanine loading tests, GTP-CH-1 activity tests, Genomic screenings are also done sometimes for definite diagnosis and genetic counselling.

Treatment

DRD is treated with levodopa, but the outcome depends upon exact doses and regimens. Some patients improve completely, some have residual symptoms depending upon the dosage and timing of treatment, and some may develop levodopa-induced dyskinesia (LID). The DRD patients are prone to LID 20 times more in comparison to other patients. In patients with GCH1 mutations, the response to levodopa is phenomenal. 50 - 200 mg levodopa daily, with a combination of peripheral decarboxylase inhibitor (carbidopa), provides outstanding result. Along with levodopa, controlled-release levodopa, several dopamine agonists and anticholinergic drugs, such as trihexyphenidyl, can also be effective [18,19]. Autosomal recessive GTP-CH-I deficiency phenotype also shows good response to levodopa therapy along with the dominant phenotype. In early childhood, treatment of this condition usually requires higher doses (~6 - 10 mg/kg daily) [20]. In patients with spasmodic dysphonia, very high doses, up to 600 mg daily might produce an incomplete response [21,22]. Levodopa-related motor complications are uncommon in this group. Even after prolonged therapy of levodopa, off dyskinesia rarely occurs in these patients [22]. Levodopa-induced dyskinesia (LID) usually presents at early treatment and is the result of very high doses [23]. Like PD, amantadine can be used to treat levodopa-induced dyskinesia in GTP-CH-I deficiency [24]. Patients with type A tyrosine hydroxylase deficiency respond well to of levodopa therapy. Oculogyric crisis, resolves completely, with mild or no residual impairment. In paediatric patients with type A tyrosine hydroxylase deficiency, the dose of levodopa is 3 - 10 mg/kg daily, divided into three doses. Patients with the type B condition are sensitive to levodopa, so initial doses are low i.e. 0.5 mg/kg daily [25].

Conclusion

The most common pathological cause of DRD is GTP-CH-I deficiency; due to this the term DRD has become synonymous with the biochemical terminology. The presentation which includes lower-limb onset of fluctuating action dystonia with diurnal variation, can

generalize over time, and shows a phenomenal and well sustained response to low-dose levodopa with combination with peripheral decarboxylase inhibitor therapy. It very often mimics cerebral palsy. Many patients are treated as a case of cerebral palsy usually. Early diagnosis and appropriate treatment can provide better outcome.

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