



DOPA Responsive Dystonia Due to GTP Cyclohydrolase -1 Deficiency Caused by PTS Gene Mutation

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Abstract

Dopa-responsive dystonia (DRD) is a childhood-onset dystonic disorder, Characteristic symptoms include dystonia typically absent in the morning or after rest but worsening during the day and with exertion. Few patients may present with signs of Parkinsonism that may include bradykinesia, rigidity, balancing difficulties, and postural instability. The striking feature of this disorder is gradual progression to generalised dystonia without significant involvement of autonomic and sensory system. Intellect also remain remarkably unaffected. Though the features typically present in first decade of life there are cases which have been reported in later decades of life. The diagnosis is usually established in patients having typical clinical features responding dramatically to oral administration of levodopa. The confirmation of diagnosis depends upon confirming mutation involving the PTS (pyruvoyl tetrahydropterin synthase) gene (Chr11:112104186; G>T).

Though genetic testing is required for confirmation of diagnosis more than 25% of patients with DRD do not show the common mutations. Some of these coding region mutation-negative cases may be due to sporadic mutations, autosomal recessive variety of DRD and TH-deficient DRD. Gene deletions, De novo mutations and incomplete penetrance may be responsible for sporadic cases. In minority of the cases metabolism of dopamine is altered but their neurological functions remain normal and these patients may behave like asymptomatic carriers of mutated genes.

Here by we present a case of DRD in a 7 year old male child with dystonic tremors and bradykinesia and was proven to have homozygous missense variation in exon 6 of the PTS gene (Chr11:112104186 ; G>T) that results in the amino acid substitution of Tyrosine for Aspartic acid at codon 116(p.D116Y; ENST00000280362). The patient responded well to L-Dopa.

Keywords: *Dopa responsive dystonia , Parkinsonism, Bradykinesia, PTS gene, L-Dopa.*

Introduction

Dopamine-responsive dystonia (DRD), also known as dopa-responsive dystonia or as heredi-

tary progressive dystonia with diurnal variation (HPD), is an inherited dystonia typically presenting in the first decade of life (although it may present in the second to early third decades, or even

later) ^[1]. It is characterised by diurnal fluctuations, exquisite responsiveness to levodopa, and mild parkinsonian features, as well as by striatal dopamine deficiency with preservation of the striatonigral terminals ^[2]. Dopamine is produced from tyrosine by the action of tyrosine hydroxylase (TH), which uses tetrahydrobiopterin (BH4) as a cofactor. BH4 is also a cofactor for tryptophan and serotonin synthesis, as well as for the enzyme nitrous oxide synthetase ^[3].

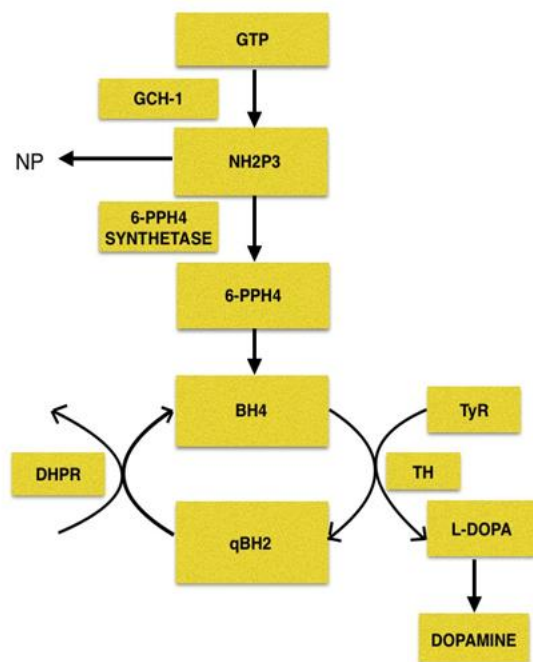


Figure 1 : Pathway showing Dopamine Bio-Synthesis.

The biochemical step of conversion of guanosine triphosphate to dihydroneopterin triphosphate requires GTP cyclohydrolase. Various mutations are responsible for deficiency of in effective production of this enzyme ^[4]. The defect in conversion of guanosine triphosphate to dihydroneopterin triphosphate is primarily responsible for dopamine responsive dystonia (DRD). This principally involve striatonigral pathway with relative sparing of neurons. This selective affection of striatonigral pathway leads to classical clinical features of bradykinesia, rigidity, balancing difficulties, and postural instability progressing to dystonia ^[5].



Figure 2 : Critical Step requiring GTP cyclohydrolase 1.

The diurnal variations are characteristic of this disease with the symptoms being less severe in the morning and worsening symptoms on exertion. These diurnal variations are not specific to DRD as these variations may be seen in any disorder affecting striatonigral pathway. The signs and symptoms classically respond to oral administration of L-Dopa ^[6]. Not all patients having DRD present with classical features and there is a wide spectrum of atypical signs and symptoms such as Psychomotor delay, seizures, systemic and cerebellar involvement may be present in many patients. Early onset DRD mimicking cerebra palsy and adult onset DRD behaving like parkinsonism is also known ^[7].

Our patient had dystonia and bradykinesia which responded dramatically to L-Dopa. He was found to have 6-PTS deficiency. This is caused by homozygous or compound heterozygous mutations in the PTS gene. The D116G variant affecting same codon has previously been reported in compound heterozygous state in a patient with transient hyperphenylalaninemia. The D116Y is not present in both the 1000 genomes and ExAC databases. Thus our PTS variation was classified as a variant of uncertain significance.

Case Report

Our patient was a 7 year old boy who was brought to us with complaints of involuntary twisting of body and abnormal posturing involving whole body since 4 years of age. Initially these posturing and twisting episodes were involving upper limbs but gradually they progressed to involve all four limbs and consequently whole of the body. These movements were episodic and each episode lasted for 2-4 hours a day. There was no h/o birth as-

phyxia. The patient has been under treatment by a local paediatrician who prescribed Valproate. Despite being on valproate and good compliance patient had episodes of involuntary twisting. On clinical examination child had dystonic movements of all four limbs, bradykinesia and fine tremor. There were no Kayser-Fleischer (KF) rings or hepatosplenomegaly. Central nervous system examination revealed normal tone and power. Deep tendon reflexes were exaggerated and there was ankle clonus. There was evidence of bradykinesia in the form of difficulty in initiation of movements. Interlimb co-ordination was preserved. On walking the patient was walking in equines posture. No sensory deficits were observed. Investigations showed normal haemogram except for anaemia (Hb 9.5). There was no evidence of acanthocytosis. Liver and renal function tests and serum ceruloplasmin levels were normal. A computed tomography was done which was normal. EEG also turned out be normal. A provisional diagnosis of DRD was considered, Valproate was stopped and Tab. L-Dopa(110mg) was started at 55mg and gradually increased upto 165mg, symptoms improved dramatically. Diagnosis was confirmed by genetic analysis, which showed mutation involving the PTS (pyruvoyl tetrahydropterin synthase) gene Chr11:11210-4186; G>T) that results in the amino acid substitution of Tyrosine for Aspartic acid at codon 116(p.D116Y; ENST00000280362).

Discussion

Segawa syndrome, dopa-responsive dystonia (DRD) is a genetic disorder was probably first described in 1969 by Coleman is a disorder characterised by childhood onset dystonia usually affecting gait with concurrent or later development of signs of parkinsonism and a dramatic response to L-dopa[8]. It typically becomes apparent from approximately age 6 to 16^[9]. Girls are affected about 2 to 4 times more frequently than boys. Evidence suggests that approximately 10 per cent of patients with childhood-onset dystonia are affected by DRD. In many patients, the onset is charac-

terised by an abnormal, “stiff-legged” manner of walking, ankle eversion and a tendency to walk on the toes. Dystonia may also extend to involve muscles of the arms, trunk, and less frequently, the neck. In addition, DRD is typically characterised by signs of Parkinsonism that may be relatively subtle. Such signs may include bradykinesia, rigidity, balancing difficulties, and postural instability. Approximately 25 per cent also have hyperreflexia, particularly in the legs^[10].

Dopa-responsive dystonia is mostly caused by autosomal dominant mutations in the *GCHI* gene (GTP cyclohydrolase1) and more rarely by autosomal recessive mutations in the *TH* (tyrosine hydroxylase) or *SPR* (sepiapterin reductase) genes^[11]. In addition, mutations in the *PARK2* gene (parkin) which causes autosomal recessive juvenile parkinsonism may present as Dopa-responsive dystonia. Tetrahydrobiopterin (BH₄) deficiencies are a highly heterogeneous group of disorders with several hundred patients, and so far a total of 193 different mutant alleles or molecular lesions identified in the GTP cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), sepiapterin reductase (SR), carbinolamine-4a-dehydratase (PCD), or dihydropteridine reductase (DHPR) genes. In a study done on 100 subjects with motor abnormalities, eight (8%) were diagnosed as PTS deficiency and 22(22%) were diagnosed as phenylalanine hydroxylase (PAH) deficiency. All patients had normal DHPR activity. Seven kinds of PTS mutations were found in 8 patients with PTS deficiency, and 75% of the mutations were 259C→T, 286G→A and 155A→G1. Compound heterozygous or homozygous mutations spread over all six exons encoding the 6-PTS gene causes an autosomal recessively inherited variant of hyperphenylalaninemia, mostly accompanied by a deficiency of dopamine and serotonin^[12].

Dudsek et al. (2001) reported that patients with BH₄ deficiency resulting from a defect in the PTS gene presented with neurologic signs linked to impaired catecholamines and serotonin synthesis^[13]. Most infants were born small for gestational

age, and most were seen at an average age of 4 months, although symptoms sometimes became evident in the first weeks of life. Frequent symptoms of PTS deficiency resembled those of Parkinson disease, indicating a lack of dopamine in the basal ganglia. Extrapyramidal signs included characteristic truncal hypotonia, increased limb tone, postural instability, hypokinesia, choreatic or dystonic limb movements, gait difficulties, hyper-salivation due to swallowing difficulties, and oculogyric crises. There were 2 main phenotypes. The more common was the severe 'central' form, accompanied by abnormalities of biogenic amines in the CSF. These patients required a combined treatment of BH4 and neurotransmitter precursors, and needed mono-therapy with BH4 in order to maintain normal plasma phenylalanine levels. In contrast, the rare mild 'peripheral' (atypical) form of PTS deficiency was characterised by normal neurotransmitter homeostasis and moderate or transient hyperphenylalaninemia. In patients with the mild peripheral form, hyperphenylalaninemia did not recur when BH4 therapy was discontinued [14].

BH4-deficient hyperphenylalaninemia due to 6-PTS deficiency is caused by homozygous or compound heterozygous mutations in the PTS gene. The D116G variant affecting same codon has previously been reported in compound heterozygous state in a patient with transient hyperphenylalaninemia. The D116Y is not present in both the 1000 genomes and ExAC databases. Thus this PTS variation is classified as a variant of uncertain significance [15].

Conclusion

Though uncommon Dopa-responsive dystonia (DRD) should always be considered in differential diagnosis of paediatric patients presenting with signs and symptoms consistent with affection of striatonigral pathway. A prompt response to oral L-dopa may aid in diagnosis. Confirmation of diagnosis needs mutation analysis.

Conflict of interest: None

References

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