

Dopa-Responsive Dystonia with Diurnal Fluctuation: A Case Report of an 18 Year Old Nigerian

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Abstract: Dopa-responsive dystonia, also known as hereditary progressive dystonia with diurnal variation, is a genetic disease characterized by childhood or adolescent onset of dystonia and sometimes associated with parkinsonian features. This is a case report of an 18 year old Nigerian University undergraduate with features of difficulty in speaking, stiffness of the body, gait difficulties, coarse tremors and toe-walking. There was a very marked improvement of symptoms and signs within 24-48 hours of the commencement of SinemetTM (levodopa/ carbidopa) 125mg/12.5mg daily. The patient was discharged after 5 days with normal gait.

Keywords: Dopa, Dystonia, Diurnal Variations, Levodopa/Carbidopa

1. Introduction

Dopa-responsive dystonia (DRD) is a genetic disease characterized by childhood or adolescent onset of dystonia and sometimes associated with parkinsonian features. It is also known as ‘hereditary progressive dystonia with diurnal variation’ or ‘Segawa’s syndrome’. It was first described by Segawa *et al* in 1976 [1, 2]. The dystonia characteristically has diurnal variations, typically reduced or absent in the morning, with sleep or after rest, but worsens during the day and with exertion. The diagnosis is based on the marked and sustained response to low doses of levodopa [1, 3, 4]. This disease is very rare affecting one in two million people. There are 25 known cases in the UK and less in Australia and New Zealand. Because of rarity, lack of awareness and low index of suspicion, it is common for this treatable disease to be misdiagnosed with avoidable consequent implications and complications [5-7]. Children with DRD are often misdiagnosed as having cerebral palsy. This article presents a case report of an 18 year old Nigerian with DRD.

2. Case Report

An 18 year old University undergraduate student was brought to the Emergency Room with complaints of difficulty in speaking and stiffness of the body. The presenting complaints were of gradual onset and dated back to six months prior to the time. There were gait difficulties, coarse tremors and toe-walking. Symptoms were said to be much relieved in the mornings and worse in the evenings. These diurnal changes were also observed while he was on admission. There was no history of fever, upper respiratory tract symptoms, change in bowel habit, body rash, seizure, headache, neck pain or neck stiffness. No history of trauma to the head. He was born after a full-term pregnancy through normal vaginal delivery to non-consanguineous parents and he was fully vaccinated according to the Nigerian Federal Ministry of Health recommendations. The development milestones were normal. No family history of similar illness or of any neurological, psychiatry or hepatic disease. He was not a cigarette smoker neither was there history of substance abuse.

Physical examination showed a conscious and well oriented young man with no pallour, jaundice, cyanosis, skin rash, peripheral lymph node enlargement or digital clubbing. The axillary temperature was 36.8°C. Central nervous system examination revealed coarse tremors and rigid posture. The head was slightly flexed and the feet rotated inwards with dorsiflexion of the great toes. The cognitive function was normal and no cranial nerve deficits. There was hypertonia of all the limbs and exaggerated deep tendon reflexes with ankle clonus. However, power was normal in all the limbs. Gait abnormality with walking in an equinus posture was unequivocal and the diurnal variations in the severity of the symptoms were observed and while on admission. No sensory abnormalities. Abdominal examination was normal. Other systems were also normal.

Full blood counts, serum electrolytes, urea and creatinine, and serum alanine transaminase, aspartate transaminase, alkaline phosphatase, bilirubin protein and albumin are within the limits of normal. The initial differential diagnoses were one, a type of a spastic disease and two, hysteria. It was after a neurological consultation that the diagnosis of a DRD was suspected. He was subsequently placed on SinemetTM (levodopa/ carbidopa) 125mg/ 12.5mg daily. There was a very marked improvement of symptoms within 24-48 hours of the commencement of the drug confirming levodopa responsiveness. The patient was discharged after 5 days with normal gait. He has resumed attending classes in the University. He has also visited the medical out-patients clinic for follow up and he had normal neurological examination.

3. Discussion

Dopa-responsive dystonia is an inherited disease typically presenting in the first decade of life. It may also present in the second and third decades or even later. Several cases of late-onset DRD have been published [8-10]. It is characterized by mild parkinsonian features with diurnal fluctuations and marked response to treatment with levodopa. It was first described by Segawa *et al* in 1976 [1]. This disease is very rare affecting one in two million people. It is more frequent in females than males [8, 9].

In DRD, there is selective deficiency of striatonigral dopamine without neuronal loss caused by genetic defects in dopamine synthesis. Dopamine is produced from tyrosine by the action of tyrosine hydroxylase (TH) which uses tetrahydrobiopterin (BH4) as a cofactor (11). BH4 is synthesized from guanosine triphosphate (GTP) by GTP cyclohydrolase I (GCH), 6-pyruvoyltetrahydropterin synthase (PTS), and sepiapterin reductase (SPD). GCH is the rate-limiting enzyme. Mutations in the genes for GCH and TH are responsible for autosomal dominant and autosomal recessive DRD respectively [12-15].

The clinical features that would be described here are those associated with autosomal dominant DRD. The most common presenting symptom of DRD is a gait disturbance with leg stiffness and the characteristic tiptoe (equines posture) walking pattern. The dystonia usually starts with a

limb and, with the disease progression; it spreads to involve the trunk and all the four limbs. Bradykinesia may develop due to failure of reciprocal innervation resulting from the dystonia. There are other features such as hypertonia of the muscles, exaggerated deep tendon reflexes, flexor plantar reflex and striatal toe [16]. Characteristically, the patients experience diurnal aggravation of the disease with no or less symptoms in the mornings [16, 17]. In autosomal recessive DRD from TH or sepiapterin reductase deficiency, motor and mental developmental delay is common.

A close differential diagnosis of clinical features of DRD is early onset idiopathic parkinsonism with dystonia. However, this presents in the fourth decade while DRD occurs in childhood. In addition, the sustained response of DRD to levodopa without adverse effects differentiates it from early onset parkinsonism with dystonia. In childhood, DRD may be misdiagnosed as cerebral palsy or spastic diplegia [18]. In early onset dystonia, Wilson disease, Hallervorden-Spatz disease and neuroacanthocytosis should be considered. Focal variations of DRD such as spasmodic torticollis or oromandibular dystonia should be differentiated from idiopathic (dopamine-nonresponsive) focal dystonias with a therapeutic trial with levodopa [17]. Other differential diagnoses include primary dystonic juvenile parkinsonism and dyspeptic dystonia with hiatal hernia.

Although DRD's diagnosis is made from a typical history, a trial of a levodopa and genetic testing (which is not sine qua non as not all patients show mutations in the GCH1 gene), however, some laboratory and imaging investigations may be important to rule out differential diagnoses. For example, full blood count with peripheral smear examination to rule out acanthocytosis. Others are serum studies for blood urea nitrogen (BUN), creatinine, liver function, copper and ceruloplasmin, and cerebrospinal fluid studies. Cerebrospinal fluid pterins may be important in distinguishing the three entities that are responsive to levodopa: GTPCH-deficient DRD (decreased biopterin and neopterin), TH-deficient DRD (normal biopterin and neopterin) and early-onset parkinsonism (reduced biopterin and normal neopterin) [19, 20]. In about half of cases, a phenylalanine loading test can be used to show decrease conversion from the amino acid phenylalanine to tyrosine. This process uses BH4 as cofactor. Molecular biology can confirm the diagnosis in some cases [21]. Brain magnetic resonance imaging may show abnormalities in the basal ganglia suggesting Wilson disease or Hallervorden-Spatz disease. Positron emission tomography scan uptake of fluorodopamine (¹⁸F) may be decreased in early onset Parkinson's disease but it is normal in DRD [22-24]. Single-photon emission computed tomography (SPECT) scanning with iodine-123 (¹²³I) 2 beta-carbomethoxy-3beta-(4-iodophenyl) tropane (b-CIT) can also differentiate DRD (normal) from early onset Parkinson disease (reduced) [25].

The cornerstone of the treatment of DRD is the use of levodopa/carbidopa combination. There is typically marked, long-term response to low-dose levodopa. The optimal dose differs among patients: while some respond markedly to

small doses, others require higher doses. De la Fuente-Fernandez reported adequate control with a daily dose of 250 mg of levodopa [26] while Wang *et al* suggested an optimal dose of 10 mg/kg [27]. Others have reported control with 20 mg/kg (28) or 100 mg/d (29). Early treatment can prevent complications such as contracture formation and fixed equinovarus foot deformity. In patients with autosomal recessive TH deficiency, early treatment with levodopa may also reduce the motor and intellectual developmental delay. Surgery may be done to release contracture and to correct foot deformity after treating the dystonia with levodopa. Physical therapy is also important if there is contracture or chronic gait disturbance [30]. Beside levodopa, other effective drugs include anticholinergic agents, such as benztropine; carbamazepine, BH4, 5-hydroxytryptophan and botulinum toxin injection for resistant cases of focal dystonia.

The prognosis for patients with DRD is good with adequate and early treatment. Limb contractures and growth retardation can occur in untreated patients. There is no data on mortality associated with DRD, but patients surviving beyond the fifth decade with treatment have been reported [26, 31].

4. Conclusion

This is a case report of an 18 year old Nigerian with presenting features of difficulty in speaking, stiffness of the body, gait difficulties, coarse tremors and toe-walking. The clinical diagnosis was suspected and made after neurological consultation. There was an exquisite response with very marked improvement of symptoms and signs within 24-48 hours of the commencement of SinemetTM (levodopa/carbidopa) 125mg/ 12.5mg daily, and the patient was discharged after 5 days with normal gait.

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