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ABSTRACT

Dopamine responsive dystonia (DRD) is a dystonic syndrome of childhood, usually affecting gait. It presents with walking difficulties, spasticity or dystonia with a characteristic diurnal variation and MRI brain scan is normal in it. It may however develop into Parkinsonism later, which shows dramatic therapeutic response to levodopa.
A 25 year old lady presented with difficulty in walking along with weakness and stiffness of both legs at Neurology OPD of Chandka Medical College Hospital,Larkana. After reaching at proper diagnosis of DRD, treatment was started. As a result of which, she showed dramatic improvement and was able to return back to her routine life.

INTRODUCTION

Dopamine-responsive dystonia (DRD), also known as dopa-responsive dystonia or as Segawa disease, is an inherited autosomal dominant dystonia typically presenting in first decade of life (although it may present in second to early third decades, or even later). It is characterized by diurnal fluctuations, exquisite responsiveness to levodopa, and mild Parkinsonian features, as well as by striatal dopamine deficiency. The signs of Parkinsonism are relatively subtle in DRD. These signs may include slowness of movement, stiffness and resistance to movement (rigidity), balance difficulties and postural instability. These Parkinsonian features often respond well to regular doses of levodopa (a synthetic form of the brain chemical, dopamine).

CASE REPORT

A 25 year old lady presented in the outpatient department of a tertiary care hospital atLarkana, Pakistan with chief complaints of difficulty in walking, weakness and stiffness of both legs for three years. According to the patient's attendant she was in her usual state of health three years back when she first observed difficulty in walking which then increased slowly & gradually. After some time owing to unsteady gait, she started using acane. But her condition sub-vitals. Her higher mental functions and cranial nerves were intact. On motor examination, she had normal bulk, tone, power& reflexes in both upper limbs.Whereas in lower limbs, bulk was normal and tone was increased (legs were spastic on touching and remained in that position for few seconds & then resolved itself). Power was 0/5 in lower limbs. However, reflexes were normal with flexor planter response. Sensory system & Cerebellar system were intact and gait was not assessed.Whereas, rest of the systemic examination was unremarkable.On slit lamp examination, noKayser-Fleischer ring was found and fundus examination was normal too.
Her complete blood count, ESR, electrolytes, serum calcium level, vitamin D level, liver function test, urine detail report were normal, the serum cerulopalsmin& 24hour urinary copper level were in normal range. Her radiographic studies chest x-ray, lumbo-sacral spine, CT scan brain were unremarkable, MRI lumbo-sacral spine was also normal.
Sinemet12.5mg/50mg (L-dopa 50 mg + Carbidopa 12.5 mg) was startedat a dosage of half tablet twice worsened further&shebecame completely immobile. She, however, had full control of her sphincters.There was no other such similar family history. Birth history of the patient was unremarkable and developmental milestones were normal too with proper immunization history.

On Examination, patient was conscious. She was oriented to time, place & person with stable vitals and

DISCUSSION

Dopamine responsive dystonia (DRD) encompasses a group of clinically and genetically heterogeneous disorders that typically manifest as limb-onset, diurnally fluctuating dystonia and exhibit a robust and sustained response to levodopa treatment. Autosomal dominant GTP cyclohydrolase 1 deficiency, also known as Segawa disease, is the most common and best-characterized condition that manifests as DRD. Dopamine responsive dystonia (DRD) is estimated to affect 1 per million people worldwide. Mutations in the GCH1 gene are the most common cause of dopa-responsive dystonia. Less often, mutations in the TH or SPR gene cause this condition.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. The first rate-limiting step for BH4 synthesis is GCH. The gene for GCH has been cloned to 14q 22.1-22.2 and is the gene responsible for autosomal-dominant DRD/HPD. Mutations in the *GCH1* gene are found across the entire gene; 99 of the 104 mutant alleles are present in a heterozygous state and cause DRD in a dominant fashion with reduced penetrance. [2] More than 50% of patients with autosomal-dominant inherited DRD have mutations in the *GCH1* gene.[3,4,5,6,7]

Point mutation in the gene for SR has been detected in patients who have autosomal-recessive DRD. SR-related DRD has been shown to be similar to, yet somewhat more severe than, TH-deficient DRD.[8]

Despite advances in the understanding of DRD, genetic testing is not definitive. Thirty percent to 40% of patients with DRD do not show the common mutations.

Girls are affected more than boys with ratio of 2 or 3:1. The most common presenting symptom of dopamine-responsive dystonia (DRD) is a gait disturbance. These patients may be misdiagnosed as having cerebral palsy. Typically, the dystonia starts in 1 lower limb (with evening exacerbation), resulting in a tiptoe (equinus) walking pattern. Early in the disease course, patients are symptom free in the morning. Diurnal aggravation of symptoms depends more on the number of waking hours than on physical activity. The disease progresses markedly in the first 15 years, with postural dystonia progressing to all 4 limbs (even in the morning) by the end of the second decade. Progression slows in the third decade and plateaus thereafter. [21] The dystonia is variable in severity, depending on the duration of disease prior to treatment. Gait disturbance is characterized by leg stiffness and a tendency to walk in an equinus posture. The great toe is dorsiflexed. Gait tends to worsen later in the day. With increasing age and without treatment, dystonia spreads to involve the trunk and all 4 extremities.

Postural tremor, which is not observed in childhood, appears after the third decade. Resting tremor and rigidity are absent, and inter limb coordination is preserved (even in advanced cases).

Bradykinesia may develop. This is not due to failure of initiation and poverty of movement as in Parkinsonism; rather, it is due to failure of reciprocal innervation resulting from the dystonia.

Muscle tone is increased and deep tendon reflexes are exaggerated (with ankle clonus). The plantar reflex is flexor, although striatal toe is common. [21]

DIAGNOSIS

The diagnosis of DRD is not made by one definitive test, but by a series of clinical observations and specific biochemical assessments. Defining the exact cause may not be possible.

A therapeutic trial with levodopa remains the most practical initial approach to diagnosis. Even an adverse reaction may help illuminate details about the cause and warrant additional tests, and not all DRD patients respond to levodopa immediately. Furthermore, not all individuals who are carriers will exhibit symptoms. A detailed family history is an important element of diagnosis.

Obtaining a cerebrospinal fluid sample (via lumbar puncture) is an important component of diagnosing DRD. This may be the most straightforward way to obtain a preliminary diagnosis and distinguish among possible metabolic conditions. There remains a chance that the cerebrospinal test will not provide a definitive diagnosis. It is crucial that the patient stop taking levodopa at least a week before the cerebrospinal fluid collection.

Specific metabolic defects may be detected by an oral phenylalanine loading test, but the test is not 100% sensitive and the scope is limited. False negatives may occur with this test, detecting only about 80% of cases of DRD. Similarly, there are tests for very specific metabolic conditions that do not address the entire scope of possible deficiencies.

DRD must be distinguished from other disorders with similar symptoms including cerebral palsy, early-onset generalized dystonia, spastic paraplegia, and disorders which cause childhood-onset parkinsonism. Patients and family members should understand that diagnosing DRD can be challenging, but that there are steps toward differentiating among the various types.

TREATMENT

Symptoms of DRD can usually be treated effectively with a drug called levodopa, and most often a combination of levodopa and carbidopa. In many cases, full physical functionality including walking, running, speaking, and writing is restored or preserved.

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