CASE REPORT

Delayed Diagnosis of Dopa-responsive Dystonia in Two Siblings

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Background: Dopa responsive dystonia is characterized by progressive disabling dystonia, diurnal variation and a dramatic response to Levodopa. **Case characteristics:** Two siblings presented with regression of motor milestones and hypertonia in lower limbs. History of diurnal variation was present in elder sibling. **Outcome:** Both responded dramatically to Levodopa. The genomic DNA analysis of elder sibling revealed a novel mutation. **Message:** A trial of Levodopa should be considered in a child with motor regression with diurnal variation, in the presence of extrapyramidal features.

Keywords: *Dystonic disorders, Extrapyramidal features, Levodopa, Parplegia.*

Dopa-responsive dystonia (DRD) or Segawa disease is a rare inherited disease that presents with progressive disabling dystonia at variable ages. A typical feature of this condition that differentiates it from other primary dystonias is diurnal variation, with worsening of symptoms as the day progresses. Dramatic response to levodopa is another characteristic feature [1,2].

Although dystonia is a primary feature, some children have predominant hypertonia with hyperreflexia involving lower limbs, thus mimicking diplegic cerebral palsy, hereditary spastic paraplegia or a neuro-degenerative disorder [3-9]. We herein present a report of two siblings with unusual presentation and having a novel mutation.

Case Report

A 4-year-6-month-old female presented with inability to sit straight and walk for last 3 years. She was a product of non-consanguineous marriage with an uneventful perinatal history. She achieved sitting balance at six month of age; however, intermittent tremors were noted in the head while sitting and in the legs while lying down. She achieved walking with support at the age of 10 months, but over next two months she started having frequent falls. In another two months she could not walk, and while sitting, she was noted to have forwards or backwards bending of body with forward bending of head. She continued to be the same till the time of presentation. She was able to use her hands though the movements were slow. Her cognitive and speech domains remained unaffected; though, speech was slow with difficulty in initiating words. At around 3 years of age, she could walk with support, crawl and sit upright for around 30 minutes, immediately after waking up in the morning. She could also do the same for few minutes after a daytime nap.

On examination, the child could sit with trunk bent forwards and head falling forwards. She could lift her head intermittently on command. Speech was intelligible but slow. There were intermittent resting tremors of the head and lower limbs. Cranial nerve examination was normal. Tone was increased bilaterally in lower limbs, especially in tendoachilles muscles with bilaterally brisk deep tendon reflexes and extensor planter responses.

The younger sibling, a 2-year-11-month-old female was also noted to have tremors involving lower limbs and head at the age of 4-5 months. Sitting balance was achieved at 9 months of age but there were frequent falls while sitting and mild forward bending of back with neck bent backwards or sideways. She could walk with support at 12 months with back and neck bent. There was no further gain in motor milestones. Her speech and cognition were also normal. No diurnal variation was noted. On examination, toe walking was present with hypertonia and brisk deep tendon reflexes in lower limbs.

Over the years, both siblings had visited many physicians, with the diagnosis of cerebral palsy mentioned by some. A third sibling, a 14-months-old-male was presently normal. In view of the clinical findings, a differential diagnosis of hereditary spastic paraplegia and white matter disease was considered and investigations were planned. MRI brain and nerve conduction studies of both siblings were essentially normal. Results of serum lactate levels, blood tandem mass spectrometry, and urinary gas chromatography mass spectrometry were also normal.

In view of lower limb lead-pipe type of rigidity, with

dystonia of neck and trunk resulting in bending, along with diurnal variation in elder sibling, and presence of tremors, a possibility of DOPA-responsive dystonia was considered and a trial of Levodopa 0.4 mg/kg (with Carbidopa) was given to elder sibling. Within days of therapy, she started standing without support and walk with support; though, some abnormal movements were noted. On a follow-up 5 days after starting Dopa, she had generalized chorea. On same treatment the chorea disappeared within 10 days. She subsequently showed rapid gain in motor milestones and examination revealed only mild rigidity of tendo-achilles with normal deep tendon reflexes. After 6 weeks, the dose of Levodopa was increased to 0.6 mg/kg. Within next 4 weeks, the child could do all the activities comparable to her peers. The younger sibling also showed a similar response to levodopa though there was no chorea. At 21 months after diagnosis, both children are attending school with age-appropriate development.

The elder sibling's blood sample was sent for genomic DNA analysis for mutation in *GTP Cyclohydrolase1* gene *(DYT-5*) by gene sequencing. Heterozygosity for the allele P.K 160 E was detected. This was a novel variation, predicted to be damaging by the bioinformatics software Mutation Taster.

DISCUSSION

This report highlights the need to consider Dopa-responsive dystonia as a differential diagnosis and elicit a history of diurnal variation, whenever a child presents with motor regression with hypertonia involving lower limbs. The presence of early tremors and neck/truncal dystonia should also alert the physician to the extrapyramidal origin of the disease. The dramatic response of this severely disabling condition to Levodopa makes it critical to diagnose.

DRD is an autosomal dominant disease caused by GTP cyclohydrolase deficiency 1 (GCH1) due to heterozygous mutation *of GCH1* gene on chromosome 14q22.1 to q22.2. More than 100 mutations have been identified in the coding region of the causative gene; however, around 40% patients have no known mutations [1,10]. About 30 percent cases are sporadic occurring due to *de novo* mutations [9]. The penetrance of this condition is low (30-40%) with a female preponderance in the ratio of 2-3:1 [1]. This probably explains the occurrence of this condition in only two female siblings of this family. Rarely, some patients of DRD manifest mainly as rigidity of lower limbs with hyperreflexia and ankle clonus mimicking spasticity. There are reports of children presenting with tip-toe walking and a misdiagnosis of spastic diplegic cerebral palsy. Other common misdiagnoses are hereditary spastic paraparesis and neurodegenerative disorder [3-9].

To conclude, a high index of suspicion for Dopa responsive dystonia should be there whenever one encounters a case of "atypical" cerebral palsy. The dramatic response to Levodopa confirms the diagnosis in all cases.

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