CASE REPORT

Segawa Disease: Report of Cases from Quetta and Review of Literature

MOBIN-UR-REHMAN[1], S. LIAQUAT ALI KHAN[2], BASHIR ULLAH[3]

SUMMARY

Segawa disease also known as Dopa-responsive dystonia is one of the treatable causes of Dystonia. It is rare but may have many unusual features. We present the spectrum of presentations of DRD as came to our experience at this centre.

INTRODUCTION

Dopa-responsive dystonia (DRD) is a clinical syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of levodopa[1]. Dopa-responsive dystonia (DRD) is an eminently treatable condition and its recognition is therefore of crucial importance. In classical cases, the disease manifests in early childhood with walking problems due to dystonia of the lower limbs[2]. They have dramatic and sustained response to levodopa[3].

Case 1: A 9 month old child was referred to us for delayed mile stones. He had started neck holding at 5 months and was not sitting yet at the time of presentation. He was diagnosed as a case of benign congenital hypotonia. He was also empirically started L- Dopa, and after two months of therapy the patients started sitting. After three months of therapy he was standing with support.

Case 2: A five year old girl presented to us with the history of delayed sitting, standing and speech. She had been lethargic since birth, with reduced movements and hypotonia. Earlier the baby had difficulty during breast-feeding. During these six years she was shown to multiple doctors and was labeled Cerebral Palsy. When she was brought to our hospital, she was started carbidopa in the dose of 10 mg OD, marked improvement was noted: she could stand by three months of therapy and started going to school by one year of therapy.

Case 3: A one year old boy presented with history of delayed cry and cyanosis at birth. He sat at 9 months and crawled at one year. He can speak few sentences and could transfer objects and could hold a cup. He was receiving symptomatic treatment. He was empirically given L-dopa. He started walking after one month. And then he had normal motor examination.

[1]Assist. Professor Paediatrics, [2]Assist. Professor Nephrology, [3]Assist. Professor of Medicine, Bolan Medical College, Quetta

Correspondence to Dr. Mobin-ur-Rehman. Email: mobin38@gmail.com

Case 4: A one year old boy presented with delay in motor milestones. He was not able to sit or stand. He was born premature, with uneventful birth history. On examination he had increased tone and decreased power in his lower limbs while tone, power, reflexes were normal in the upper limbs. He was started L-Dopa. After two months of therapy the tone in his lower limbs improved and power become grade 4/5. The patient was able to sit with support within three months of therapy.

Case 5: A 4 month old female child presented with bringing up milk and in the process arching her back. She was initially treated with anti motility agents and acid suppression, for gastro-oesophageal reflex, but the symptoms persisted. She was empirically treated with L-Dopa and within a month she improved, demonstrating DRD.

Case 6: A nine months old infant with discoloured hair and edema of feet, developed tremor at rest. He was thought as suffering from infantile tremor syndrome and given a trial of folic acid and B_{12} but he did not improve. A further trial with phenobarbitone also failed. Then he was empirically given L-Dopa and responded within fifteen days.

Case 7: A nine year old boy was brought to us with history of worsening gait. His neurological examination revealed normal tone and reflexes. But his mother complained of inversion of feet and worsening of gait at night. A presumptive diagnosis of DRD was made and he was started on L-Dopa. Marked improvement was seen within a month.

DISCUSSION

Hereditary progressive dystonia with marked diurnal fluctuation (HPD) (also known as dopa responsive dystonia) is a dystonia with onset in childhood that shows a marked response without any side effects to levodopa[4]. There are at least three causative genes for DRD: (1) the GCH1 gene on chromosome 14q22.1-q22.2, which encodes GTP cyclohydrolase I

(GTPCH), the first enzyme in the biosynthetic pathway for tetrahydrobiopterin (BH4; the essential cofactor for tyrosine hydroxylase [THl]), (2) the TH gene on 11 p15.5, coding for the enzyme TH that catalyzes the rate-limiting step in the catecholamine biosynthesis, and (3) an as yet undefined gene on 14q13 (DYT14)[1].

The usual age of onset is 10±3 years. Onset occurred earlier in female 9±4 years than in male 12±1 years.[3] The classic phenotype was most frequent (n=23), with female predominance (F:M=16:7), and early onset (mean 4.5 years) with involvement of legs[5.]. Wang described a subset of patients with age at onset ranged from 18 months to 8 years, and a female predominance of 4:2[6]. DRD usually starts as a foot dystonia with gait difficulties and subsequent overflow of dystonic movements to other muscles and parts of the body, with parkinsonian features and pyramidal signs in part of cases. Diurnal fluctuations with deterioration in the evening are typical for DRD[7]. Other presentations may be with mild postural tremor and postural dystonia manifested initially by flexion-inversion of a foot.[6] The presentation may be typical with craniocervical dystonia, spasmodic dysphonia, early hypotonia delay in motor development, early hypotonia delay in motor development, wadding gait, generalized hypotonia, and proximal weakness since early childhood and dystonia during feeding.[8-11] Kamal[12] has described a case with 12 year old boy with gradually worsening global developmental delay was diagnosed and managed as quadriplegic cerebral palsy since child-hood. Fletcher has suggested that a therapeutic trial of levodopa is advised in all patients in whom dystonia has developed in childhood or early adult life, regardless of suspected etiology or duration of symptoms.[13] DRD must be considered in the differential diagnosis of the child or adolescent presenting with a dystonic gait disorder, diplegic cerebral palsy, sporadic spastic paraplegia, ataxic syndromes, and juvenile parkinsonism[14].

The phenylalanine loading test is used in differentiating DRD from primary focal and generalized dystonia.[15] In children with DRD, dried blood Phe/Tyr ratio exceeded 4.6 (plasma Phe/Tyr ratio >5.4) after 2 h and biopterin concentration in dried blood remained below 16.2 nmol/L (plasma biopterin <14 nmol/L) 1 h after Phe challenge.[16]

The most sensitive and least costly method to diagnose DRD is a therapeutic trial of levodopa. Wang suggested that 10 mg/kg/day of L-dopa may be an optimally effective dose for treatment of patients with HPD[6]. Other workers have used doses as high as30 60 mg/day[17].

REFERENCES

1. Furukawa Y. Dopa-responsive dystonia: clinical, genetic, and biochemical studies. Clin Neurol 2006; 46: 19-34.
2. Bandmann O, Wood NW. Dopa-responsive dystonia -- the story so far. Neuropediatrics 2002; 33: 1-5.
3. Xie H, Wu ZY, Wang N, Li ZW, Lin MT, Murong SX. Clinical analysis of dopa-responsive dystonia and mutation analysis of the GCH I gene. Zhonghua er ke za zhi 2006; 44: 492-5.
4. Ichinose H, Ohye T, Takahashi E, Seki N et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nature genetics 1994; 8: 236.
5. Trender-Gerhard I, Sweeney MG, Schwingenschuh P, Mir P, Edwards MJ, Gerhard A, et al. Autosomal-dominant GTPCH1-deficient DRD: clinical characteristics and long-term outcome of 34 patients. J Neurol Seurosurg Psychiatr 2009; 80: 839-45.
6. Wang PJ, Ko YM, Young C, Hwu WL, Shen YZ. Hereditary progressive dystonia with marked diurnal fluctuation (Segawa syndrome) in Taiwan. Brain Develop 1994; 16: 126-31.
7. Slawek J, Friedman A, Bogucki A, Budrewicz S, Banach M. Dopa-responsive dystonia (Segawa variant): clinical analysis of 7 cases with delayed diagnosis. Neurol Neurochir Pol 2003; 37: 117-26.
8. Bandmann O, Marsden CD, Wood NW. Atypical presentations of dopa-responsive dystonia. Advan Neurol 1998; 78: 283-90.
9. Kong CK, Ko CH, Tong SF, Lam CW. Atypical presentation of dopa-responsive dystonia: generalized hypotonia and proximal weakness. Neurology 2001; 57: 1121-4.
10. Tsirikos AI, Carr LJ, Noordeen HH. Variability of clinical expression and evolution of spinal deformity in a family with late detection of dopa-responsive dystonia. Develop Med Child Neurol 2004; 46: 128-37.
11. Chieng KS, Hussain N, Gosalakkal JA. Dystonia during feeding as an early sign of dopa-responsive dystonia. Pediatr Neurol 2007; 37: 215-7.
12. Kamal N, Bhat DP, Carrick E. Dopa-responsive dystonia (Segawa syndrome). Indian Pediatr 2006; 43: 635-8.
13. Fletcher NA, Thompson PD, Scadding JW, Marsden CD. Successful treatment of childhood onset symptomatic dystonia with levodopa. J Neurol Neurosurg Psychiatr 1993; 56: 865-7.
14. Nygaard TG, Marsden CD, Duvoisin RC. Dopa-responsive dystonia. Advan Neurol 1988; 50: 377-84.
15. Bandmann O, Goertz M, Zschocke J, Deuschl G, et al. The phenylalanine loading test in the differential diagnosis of dystonia. Neurology 2003; 60: 700-2.
16. Opladen T, Okun JG, Burgard P, Blau N, Hoffmann GF. Phenylalanine loading in pediatric patients with dopa-responsive dystonia: revised test protocol and pediatric cutoff values. J Inherited Metabol Dis 2006; ;33: 697-703.
17. Grippo J, La Fuente A, Corral SM, Grippo T. Hereditary progressive levodopa sensible: Segawa's syndrome. Revista de Neurol 2002; 34: 933-6.