Case Report

Pallidal Deep Brain Stimulation for *KMT2B* Related Dystonia in An Indian Patient

Roopa Rajan, Kanwaljeet Garg[1], Arti Saini, Mukesh Kumar[2], Binukumar BK[2], Vinod Scaria[2], Rajeev Aggarwal, Anu Gupta, Vishnu VY, Ajay Garg[3], Mamta Bhushan Singh, Rohit Bhatia, Achal K. Srivastava, M.V. Padma Srivastava, Manmohan Singh[1]

Department of Neurology, All India Institute of Medical Sciences, New Delhi, [1]Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi, [2]CSIR-Institute of Genomics and Integrative Biology, New Delhi, [3]Department of Neuroradiology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Outcomes of pallidal stimulation in *KMT2B* dystonia have been infrequently reported prospectively. We report the six-month outcomes of bilateral GPi DBS in an Asian Indian patient with early-onset generalized dystonia associated with a novel heterozygous variant in the *KMT2B* gene.

Keywords: Early-onset generalized dystonia, GPi DBS, *KMT2B* gene, variants

What is known?

Mutations in the *KMT2B* gene are increasingly being recognized in association with early onset generalized dystonia. Recent evidence suggests good response to pallidal stimulation in *KMT2B* dystonia, though few patients have been reported worldwide.

What is new?

We report the 6-month outcomes of pallidal deep brain stimulation (DBS) in an Indian patient with *KMT2B* associated dystonia. To the best of our knowledge, this is the first report of pallidal DBS for *KMT2B* associated dystonia in an Indian patient.

Introduction

Heterozygous variants in the *KMT2B* (Lysine methyltransferase 2B) gene are increasingly being identified in association with early-onset, complex dystonia phenotypes.[1] Though early reports suggest benefit with bilateral globus pallidus interna (GPi) deep brain stimulation (DBS), objective outcomes have been reported infrequently.[2,3] We report the 6-month outcomes of GPi-DBS in an Asian Indian patient with *KMT2B*-associated dystonia.

Case Report

A 17-year-old girl presented with abnormal posturing of the right upper and lower limbs since the age of 9 years, followed by involvement of left upper and lower limbs at the age of 11 years, difficulty in speaking at 13 years and abnormal neck posturing noted at 15 years of age. At the time of presentation to us, she had generalized dystonia involving the lower face, tongue, neck, trunk, and all four limbs. A bulbous nose tip was noted [See Video 1]. She was anarthric and wheelchair bound. She had normal cognition and no evidence of parkinsonism, spasticity, incoordination, extraocular movement, or other neurologic deficits. Birth and developmental history were uneventful. Her elder sibling had early onset generalized dystonia [See Figure 1e for pedigree details].

Biochemical investigations including workup for Wilson's disease were within normal limits. Cranial MRI revealed symmetrical T2 hyperintensities in bilateral posterior putamen without any evidence of mineral deposition. [Figure 1a-d]. Written informed consent was obtained from the patient for publication. Clinical Exome Sequencing revealed a novel heterozygous missense variant, c.4675G > T (p.D1559Y) in exon 20 of the *KMT2B* gene [Figure 1f]. To confirm it further, we designed primers covering exon 20 of *KMT2B* gene and performed Sanger's sequencing of the proband along with her parents. Parental screening revealed the same variant in heterozygous state in her asymptomatic mother [Figure 1f]. The variant, p.D1559Y was classified based on the joint guidelines of ACMG (American College of Medical Genetics and Genomics) and AMP (Association of Molecular Pathology) and reported as VUS (Variant of Uncertain Significance). Multiple lines of computational evidence suggested a deleterious effect on the gene or gene product. This variant was

Address for correspondence: Dr. Roopa Rajan, Room No. 704, 7th Floor, Cardio-Neuro Centre, Ansari Nagar, AIIMS, New Delhi, India.
E-mail: rooparajan@aiims.edu

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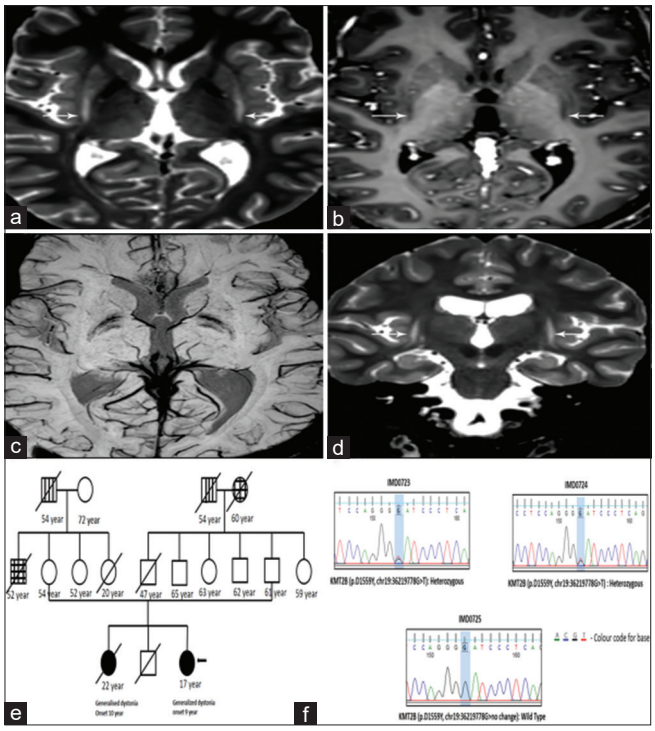

Figure 1: MRI Brain axial (a) and coronal (d) T2-weighted images show bilateral posterior putamen symmetrical atrophy and hyperintensities (arrows in a and d), which are hypointense (arrows in b) in contrast-enhanced T1-WI. No susceptibility signal is seen in Susceptibility-Weighted Imaging (c). A three-generation pedigree of the patient (e). Results of Sanger sequencing in the proband and parents confirming the heterozygous c.4675G>T (p.D1559Y) variant in the proband and her asymptomatic mother (f)

also absent from, 1029 genomes from India (IndiGenomes), SAGE (South Asian Genomes and Exomes), and other global databases including ExAC, ESP6500, GME, 1000G but observed in heterozygous form in 1 South Asian male out of 15301 samples considered for gnomAD exome with minor allelic frequency 0.000004014 (gnomAD exome all) and 0.00003268 (gnomAD exome SAS).

She had previously received levodopa upto 300 mg/day without any benefit. She was intolerant to anticholinergic drugs and was presently on tetrabenazine 75 mg/day and clonazepam 0.25 mg/day with persistent significant disability. The Burk-Fahn-Marsden Dystonia Rating Scale motor score (BFMDRS-M) was 94 (range 0-120) and BFM-Disability (BFMDRS-D) score was 24 (range 0-30). Considering the severe disability and lack of response to medical management, she was offered GPi-DBS. She underwent stereotactic guided bilateral GPi-DBS with microelectrode recording and clinical monitoring for adverse effects under general anesthesia (Activa RC^{Ó}, Medtronic, Minnesota). Immediately after surgery, there was mild improvement in the neck and limb dystonia. At 6 months follow up, after optimization of stimulation parameters, the BFMDRS-M score was 57.5 and the BFMDRS-D was 22. [See Supplementary table] She had regained ambulation with support. [See Video 1] At last follow-up, stimulation parameters for left GPi were 3(-) C (+), 1.5 V/60 µs/150 Hz and for right GPi were 11(-) C (+), 1.7V/90 µs/150 Hz.

Discussion

KMT2B associated dystonia is typically an early-onset generalized dystonia that starts in the lower limbs with prominent lower cranial or bulbar involvement eventually.[2] Dysmorphic features including a bulbous nose tip have been reported frequently in addition to intellectual disability, developmental delay, extraocular movement deficits, myoclonus, spasticity, seizures, and sensorineural hearing loss. Since the initial description of the *KMT2B* gene in association with dystonia, multiple reports have identified it to be among the commonest genes associated with early onset dystonia in dystonia cohorts.[1,4,5] Diagnosis is obtained by detection of a heterozygous pathogenic variant or 19q13.12 deletion using single or targeted panel sequencing, exome sequencing or chromosomal microarray analysis. The variant detected in our patient lies within PHD-like domain of the *KMT2B* gene, recognized as a mutational hotspot.

Dystonia is usually refractory to medical therapy and GPi-DBS has been reported to be effective with reductions in BFMDRS scores of 25-73%, especially in younger patients.[6]

Of the less than 30 patients with *KMT2B* dystonia, reported to have undergone GPi-DBS, objective dystonia rating measures were reported only in a few.[7,8] A recent report of longitudinally followed up patients reported >30% improvement in BFMDRS scores in 50% of patients at 1 year with most improvement attributable to improvement in truncal and cervical dystonia.[2,3] Of special interest is the improvement in gait and regaining of ambulation (albeit dependent) reported in several patients including ours.[9,10] Considering the available evidence of benefit and increasing recognition in dystonia cohorts, prospective follow up studies of GPi-DBS in genetically proven *KMT2B* dystonia are warranted to confirm these initial findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1

BFMDRS-M

Region	Score (Pre- DBS)	Score (6 months follow-up)
Eyes	0	0
Mouth	6	4.5
Speech/Swallowing	8	9
Neck	8	2
Right arm	12	9
Left arm	12	6
Trunk	16	9
Right Leg	16	9
Left Leg	16	9
Total	94	57.5

BFMDRS-D

Region	Score (Pre-DBS)	Score (6 months follow-up)
Speech	4	4
Handwriting	4	4
Feeding	3	3
Eating/Swallowing	0	0
Hygiene	3	3
Dressing	4	4
Walking	6	4
Total	24	22