Long-Term Efficacy of Pallidal Deep Brain Stimulation in a Patient with DYT-THAP1 (DYT-6) Dystonia from India

Dear Sir,

DYT6 is an autosomal dominant dystonia.[1,2] The disease locus was originally described on 8p21-q22 by linkage analysis in Amish–Mennonite families. However, with the improved knowledge (identification) of the disease gene, it has now become possible to identify *DYT6* location on 8p11.21. It has reduced sex independent penetrance by approximately 60%.[1] Unlike DYT1 dystonia, this form of dystonia predominantly affects craniocervical region.[1] Occasionally, the disease may begin in upper limbs, but lower limb onset of dystonia is rare. Dysphonia is commonly seen. The age of onset of symptoms is variable extending from early age to adolescents and adults. It is well proven in literature that pallidal deep brain surgery is recommended treatment for isolated generalized dystonia.[3] Few reports of successful treatment of DYT6 dystonia with deep brain stimulation surgery are now emerging.[4,5] We describe a case of genetically proven DYT6 dystonia with a good response to pallidal deep brain stimulation surgery. This patient was operated in 2007 and the benefit of surgery remained excellent at the end of 12 years. Apparently, this patient is also the first DYT6 mutation case reported from India.[6]

Case History

A 50-year-old male presented with history of difficulty in writing at the age of nine. He had difficulty in holding objects in the right hand. His symptoms remained stable till the age of forty-three when he started to progress with abnormal turning of his neck and pulling of his face. He had difficulty in speaking and swallowing. He also had difficulty in walking and could barely walk in the house. History included surgery for varicocele and tendon release. Family history was negative for any involuntary movements for dystonia.

Examination revealed marked dysarthria, involuntary turning of the neck with right torticollis and retrocollis. He had right shoulder elevation with pronated forearm and extension of both shoulders. He had marked scoliosis of the spine with flexed knee gait. He had forward bending of his trunk. He was unable to write [Video 1]. His blinded video preoperative Burke–Fahn–Marsden (BFM) severity score was 19. The blinded assessment was done only for the severity component. His preoperative MRI scan was normal. He tested negative for DYT1 mutation.

Table 1: Stimulation settings over follow-up of 12 years

Date	CH1 Case positive	Electrode	Pulse width/ frequency Hz	Amplitude	CH2 Case positive	Electrode	Pulse width/ frequency	Amplitude
2007		0,1	210/130	2.25		4,5	210/130	2.40
7/2014		0,1	210/130	2		3,4	210/130	2.0
9/2014		0,1	210/130	2.25		4,5	210/130	2.0
IPG Boston scientific 2017		1,2	210/130	2.6		9,10	210/130	2.8
2018-19		1 [30%], 2 [70%]	210/130	2.7		9 [30%], 10 [70%]	210/130	2.9

He underwent frame-based, microelecrode-guided bilateral deep brain stimulation surgery targeting posteroventrolateral nucleus of Gopi in March 2007. Pulse generator was implanted on the same day following postoperative MRI confirming correct position of electrodes. The stimulator setting [Table 1] was adjusted periodically to achieve maximal benefit with minimum side effects. Higher pulse width was used (preoperative and postoperative video recording were scrambled with other operated dystonic patients to reduce bias).

On follow-up at 12 years post-surgery, the response to deep brain stimulation is excellent and his blinded video BFM severity score is 04. The phasic component of his dystonia improved remarkably followed by slow gradual improvement in his tonic component. His trunk flexion and neck dystonia showed modest improvement [Video 2]. Since the patient had isolated generalized dystonia, post deep brain stimulation (DBS) genetic testing was performed for DYT6 mutation. At the end of 12 years, he still maintained his robust response. The rechargeable battery was placed.

The patient however died in sleep due to cardiac event in 2019.

The *THAP1* gene was screened by polymerase chain reaction (PCR) followed by sequencing. To identify mutation, the sequence obtained was compared with wild type sequence by pair-wise blast. 2-bp novel frameshift deletion mutation (c.208-209delAA; p.K70VfsX15) in THAP 1 gene was detected.[7]

Discussion

Dystonia 6 is caused by mutations in the gene *THAP1* (thanatos-associated protein). *THAP1* codes for thanatos-associated protein domain containing apoptosis-associated protein 1 (THAP1). It consists of three exons. Various missense, nonsense, and frameshift mutations, including a small insertion/deletion, have been described.[1,2] All three exons can be affected. Molecular pathology suggests THAP1 is composed of an N-terminal THAP (thanatos-associated protein) domain. The mutations affect THAP1 function, mainly its DNA-binding capacity and nuclear translocation. Recent reports of gene mutations indicate that DYT6 might turn out to be the second most common pure monogenic dystonia.

DYT6 dystonia often presents with isolated dystonia or involves the upper half of the body, including laryngeal adductor-type dystonia during late childhood or adolescence, and approximately 25% of patients gradually develop craniocervical involvement and generalization occurs in about 45% of mutation carriers.[3]

Our patient although had onset of symptoms at the age of nine, his symptoms worsened in adulthood and progressed rapidly causing significant disability. His worsening of the symptoms after a period of stability indicates that environmental factors play significant factor in expression of gene. His prominent symptoms were in neck, trunk, and upper limbs.

Deep brain stimulation can be a treatment of choice in these patients as reported earlier in the literature.[4-6,9]

The improvement in our patient which has sustained for the period of 12 years proves this to be effective treatment. The maximum improvement was noted in the phasic component of his dystonia. The improvement was maximum in limbs followed by trunk. His truncal lateral flexion also showed moderate improvement. Neck dystonia showed minimal improvement. This patient enjoyed the benefit of pallidal DBS surgery for the period of 12 years. This contrasts with observation in earlier literature[4] where three cases reported showed lack of sustained benefit to surgery. This in authors' opinion could be due to difference in stimulation parameters used by us [Table 1]. In a recent series, long-term benefit was seen in 2 patients at the end of 10 years.[8] Both short- and long-term outcome of DBS seems to be more variable and effective in DYT6 patients when compared to other forms of isolated genetic dystonia. The predictors of good outcome post DBS surgery in dystonia are younger age at surgery, higher disease burden, shorter duration of the disease presurgery, and fixed deformities. Speech and swallowing respond poorly to DBS.[8]

We conclude that pallidal DBS surgery is effective in all isolated dystonia irrespective of the mutations. The modest response in secondary dystonia is due to associated additional neurological features such as spasticity.

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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