Case Report

Dystonia Deafness Syndrome: A Rare Deep Brain Stimulation Responsive Dystonia

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Abstract

Dystonia deafness syndrome (DDS) is a rare syndrome characterized by childhood onset sensorineural deafness followed by adult-onset dystonia. We here report the first case of DDS from India caused by *ACTB* gene mutation presented with deafness, generalized dystonia and scoliosis who showed improvement after Deep brain stimulation.

Keywords: Deafness, deep brain stimulation, dystonia

Introduction

Dystonia deafness syndrome (DDS) is a rare clinical entity with dystonia preceded by sensorineural deafness. The etiology varies and is caused by various genetic and acquired causes. *ACTB* mutations are one of the causes of DDS. Specifically p.Arg183Trp mutation has been described previously in nine patients worldwide and may identify deep brain stimulation (DBS) responsive DDS syndrome. We herein report the first case of DDS from India caused by *p.Arg183Trp* mutation in the ACTB gene.

Case Report

A 27-year male born of nonconsanguineous parentage had sensorineural hearing loss and speech abnormality since birth. Initially, he developed focal dystonia in the form of a writer's cramp at 19 years of age for which he received periodic botulinum toxin injections for 3 years. Later he gradually developed generalized dystonia involving neck, trunk, and right lower limb and he was wheelchair bound at 27 years. There was a positive family history of dystonia (his maternal uncle had dystonia of both Upper Limb (UL) and Lower Limb (LL)). On examination, he had normal cognition, dysarthric speech (tongue dystonia), sensorineural deafness, dystonia of tongue, neck, trunk, and right lower limb. The unified dystonia rating scale (UDRS) was 92. Based on these features he was classified as adolescent onset, generalized, progressive, persistent, complex dystonia (Axis 1) with probable inherited etiology (Axis 2). MRI brain was normal. X-ray spine showed scoliosis. Whole exome sequencing showed heterozygous *p.Arg183Trp* mutation in the *ACTB* gene. He was diagnosed with DDS. Bilateral Globus pallidi (Gpi) DBS was done using stereotactic frame and generalized anesthesia. Intra-op stimulation was done after lightening the anesthesia and checking for side effects. After 3 months postoperative he is doing well and able to walk independently with improvement in truncal and limb dystonia [Video 1]. At 3 months follow-up his UDRS is 26 and stimulation parameters (monopolar stimulation -3rd contact bilaterally selected based on post-op MRI) are Left GPi C + 3-(3rd contact) 2.0 mA current, 90 us pulse width and 130 Hz frequency and Right Gpi C + 11- (3rd contact), 2.0 mA current, 90 us pulse width and 130 Hz frequency.

Discussion

DDS is a rare clinical entity with sensorineural deafness occurring before dystonia and caused by various genetic and nongenetic causes. Kojovic *et al*. studied 20 patients with the association of dystonia and deafness. They identified cause only in seven patients in spite of extensive workup. Among them, the identified genetic disorders were Woodhouse-Sakati syndrome (*C2orf37* gene mutation), Mohr-tranebjaerg syndrome (*TIMM8A* gene), organic acidurias and mitochondrial diseases, and nongenetic causes including Hypoxia/ischemic injury, central nervous system injury, or kernicterus.[1] Differentials that can be considered for DDS include 3-methylglutaconic aciduria (MEG), deafness (D), encephalopathy (E), and Leigh-like disease (L) (MEGDEL) syndrome (*SERAC1 gene*), *SUCLA2* related mtDNA depletion

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Table 1: Summary of previous patients with DDS due to *ACTB* variants

Dystonia	Deafness	Other features	Gene Involved	Management	Reference
Generalized	+	Craniofacial abnormalities, High arched eyebrows	*ACTB*	Medical + Botulinum toxin + GPi DBS	Eggink *et al*.[8]
Generalized	+	Psychiatric abnormalities, Depression, Auditory hallucinations	*ACTB*	GPi DBS	Eggink *et al*.[8]
Generalized	+	Intellectual disability	*ACTB*	Unilateral Motor cortex Stimulation	Conboy *et al*.[9]
Generalized	+	Craniofacial abnormalities, Emotional disability	*ACTB*	Gpi DBS	Skogseid *et al*.[6]
Generalized	+	Psychotic episodes	*ACTB*	Medical + Botulinum toxin + GPi DBS	Zech M *et al*.[10]
Generalized	+	Twin patients with cognitive impairment, skeletal and craniofacial abnormalities	Aggregation of Actin and Actin related proteins	Medical + Botulinum toxin	Gearing M *et al*.[7]
Generalized	+	Epilepsy, Scoliosis	*ACTB*	Medical + Botulinum toxin	Freitas *et al*.[11]
Multifocal	+	Craniofacial abnormalities, several family members were affected with craniofacial abnormalities and sensorineural deafness, patients mother also had Parkinsonian syndrome	*ACTB*	Medical + Botulinum toxin	Zavala L *et al*.[12]

syndrome, Wolfram syndrome (*WFS1* gene), and Arts syndrome (*PRPS1* gene)[2] along with *ACTB* mutation. *ACTB* mutation and *ACTG1* gene mutations were well described in Baraitser-Winter Cerebrofrontofacial syndrome (BWCFF) characterized by multiple congenital anomalies, facia dysmorphism (hypertelorism, ptosis, high arched eyebrows, broad nose), Iris coloboma, wasting of shoulder girdle muscles, sensorineural deafness, intellectual disability, and frontal predominant pachygyria.[3]

Gene *ACTB*, which encodes beta-actin protein, is an important component of the cytoskeleton which is expressed by all cells in the body with other several forms of actin.[4] *ACTB p. Arg183Trp* mutation had a gain of function effect with higher Adenosine triphosphate (ATP) hydrolysis, slower actin filament growth, and faster depolymerization with impaired formation of stable filament.[5] Skogseid *et al*. proposed that various manifestations of DDS caused by *ACTB p. Arg183Trp* mutation can be explained by specific functions of beta-actin that are compromised at different developmental stages in different cell types. These include in sequence neural crest migration and proliferation (facial dysmorphism), hair cell stereocilia function (infant onset deafness), and synaptic maintenance in the face of pubertal changes in striatal function (adult-onset dystonia).[6]

Till now this *ACTB* variant with deafness and dystonia was reported in only nine previous patients.[5-12] All had predominant sensorineural deafness and adolescent onset dystonia [Table 1] except Freitas *et al*., in their case report also reported scoliosis and epilepsy along with deafness and dystonia.[11] Among nine previously reported four underwent pallidal stimulation with beneficial effects. Skogseid *et al*.[6] demonstrated dopaminergic dysfunction as the cause of dystonia and pallidal stimulation provided sustained benefit after 4 years of follow-up.

Our patient presented with infant onset sensorineural deafness followed by adolescence onset generalized dystonia and scoliosis with *ACTB P.Arg183Trp* mutation and he was wheelchair bound at 27 years. We did bilateral GPi DBS for him and after 10 days postoperative he was able to walk without support with improvement in truncal and foot dystonia.

In conclusion to the best of our knowledge, this is the 10th case reported till date with *ACTB* mutation, and 5th case who underwent pallidal stimulation overall and first case from India. Finally in patients presented with infantile onset deafness with adult-onset dystonia must be investigated for *ACTB* mutation and DBS can be considered as a therapeutic option.

Ethical compliance statement

The authors confirm that the approval of an institution review board was not required for this work. Verbal and written consent was obtained from the patient for the publication of this case study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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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Dystonia Deafness syndrome (DDS) is a rare clinical entity with dystonia preceded by sensorineural deafness. Till now this *ACTB* variant with deafness and dystonia was reported in only nine previous patients among which only four underwent pallidal stimulation

We here in reporting the first case of DDS from India caused by *ACTB* gene mutation presented with deafness, generalised dystonia, scoliosis who showed improvement after Deep brain stimulation