Case Report

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The Significant Efficacy of Botulinum Toxin for DeafnessDystonia Syndrome Caused by ACTB Gene Mutation

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1. Abstract

Deafness-Dystonia Syndrome (DDS) is a rare and complicated disorder which can be caused by a pathogenic heterozygous mutation c.547C>T, p.(Arg183Trp) in the ACTB gene, typically leading to a combination of hearing impairment and dystonia. We presented a case of a patient with DDS associated with this mutation. Our report could further expand the phenotype of DDS, containing short stature, flattened zygomatic region and small pointed chin. In addition, compared to other patients who either experienced limited or only partial improvement by botulinum toxin injections, our patient achieved significant efficacy in the treatment of cervical dystonia, making it a valuable reference for DDS patients with focal dystonia.

2. Keywords:
Deafness-Dystonia Syndrome; ACTB; Botulinum toxin; Globus Pallidus Deep Brain Stimulation; Cervical Dystonia

3. Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions leading to involuntary movements or abnormal postures [1]. One of the most distinguishing features of dystonia from other hyperactive disorders is its close connection to movement and posture. Dystonia is often induced or exacerbated by voluntary movement. Posture abnormalities can range from spasmodic to tonic, rhythmic to fixed, or any combination. Additionally, stereotyped or patterned features of movement often accompany this disorder [2]. Deafness-Dystonia Syndrome is a rare and complex disease manifested by hearing loss and dystonia, usually accompanied by other physical or intellectual developmental impairments. Its etiology is multi-faceted, encompassing genetic, acquired and unknown causes. In particular, the genetic etiology of DDS includes Mohr-Tranebjaerg Syndrome, Woodhouse-Sakati Syndrome, organic aciduria and mitochondrial diseases [3]. So far, one patient with DDS caused by ACTB p.(Arg183Trp) heterozygosity has been reported only partial relief following the injection of botulinum toxin in his neck without undergoing deep brain stimulation [4]. We present a female with this mutation to expand the phenotypic spectrum and demonstrate a significant efficacy of botulinum toxin in the treatment of cervical dystonia in this condition.

4. Case Report

A 24-year-old women presented with congenital sensorineural deafness at age 1 and a cochlear implant was subsequently fitted in her left ear at age 8. At age 16, she experienced dystonia which began from the right hand with mild tremor and rapidly deteriorated to generalized dystonia within a year, manifesting as cervical dystonia, laryngeal dystonia and dystonic tremor in the extremities and trunk. Physical exam revealed slight developmental abnormalities, characterized by a short stature of only 145cm in height. She had mild facial dysmorphism associated with wide nasal base, flattened zygomatic region, wide mouth and small pointed chin. Moderate dysarthria was presented. Generalized dystonia was observed with cervical dystonia, laryngeal dystonia and dystonic tremor in the extremities and trunk, accompanied by weakness in the lower limbs. Her intellectual development was normal and her Mini-Mental State Examination (MMSE) score was 28, while Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) score were 3 and 8 respectively. Based on a comprehensive clinical evaluation, no significant psychiatric symptom was observed (Table 1).

Table 1: Clinical presentation, ancillary tests and treatment by age

Annals of Clinical and Medical Case Reports

Age	Clinical presentation	Ancillary tests and treatment
1 years old	Congenital sensorineural deafness	
14 months	Delayed motor development characterized by a delay in achieving independent walking	
8 years old	Delayed language acquisition and moderate dysarthria	A cochlear implant was fitted in her left ear.
16 years old	Mild hand tremors	
17 years old	Generalized dystonia (cervical dystonia, laryngeal dystonia and dystonic tremor in the extremities and trunk)	Extensive laboratory evaluations were unremarkable.
	Mild weakness in the lower limbs	
20 years old	Slight developmental abnormalities characterized by a short stature of only 145cm in height and mild facial dysmorphism associated with wide nasal base, flattened zygomatic region, wide mouth and small pointed chin	Brain CT showed no abnormalities.
21 years old	Medical treatment had limited efficacy.	Whole Exome Sequencing revealed a pathogenic heterozygous mutation in the ACTB gene c.547C>T, p.(Arg183Trp) on chromosome 7.
		Clonazepam 1mg qn, Etoricoxib 60mg qd, Eperisone 50mg tid and Levodopa 62.5mg bid
	Cervical dystonia was largely improved and has lasted for more than two years.	A total of 300 units of botulinum toxin was injected into the neck muscles.
22 years old	Dystonic tremor in the extremities and trunk was partly improved.	Escitalopram Oxalate 20mg qd, Clonazepam 1mg qn and Trihexyphenidyl1-2mg tid
24 years old	A recurrence of cervical dystonia	Toronto Western Spasmodic Torticollis Rating Scale score was 59.
	Cervical dystonia demonstrated considerable improvement and has persisted for over six months.	A total of 200 units of botulinum toxin was administered to the neck muscles.Toronto Western Spasmodic Torticollis Rating Scale score was 29.
	Dystonic tremor in the extremities and trunk was partly improved.	Vortioxetine Hydrobromide 10mg qn and Trihexyphenidyl1-2mg tid
		Hamilton Depression Scale score and Hamilton Anxiety Scale score were 3 and 8 respectively. Mini-Mental State Examination score was 28.

Extensive laboratory evaluations and brain CT were unremarkable. Given that her clinical manifestations were suggestive of DDS, Whole Exome Sequencing was carried out, revealing a pathogenic heterozygous mutation in the ACTB gene c.547C>T, p.(Arg183Trp) on chromosome 7. Neither of her parents had this mutation and her family history was negative, suggesting that it was de novo. Cervical dystonia was treated with 300 U of botulinum toxin (5 units/0.1 ml, Prosigne®, Lanzhou Institute of Biological Products, Lanzhou, Gansu, China) at age 21, 90 U for bilateral semispinalis capitis, 50 U for right splenius capitis, 110 U for left sternocleidomastoid and 50 U for bilateral cervical semispinalis. One week after injection, the neck position returned to normal and she was free of right backward torsion. She was also prescribed a daily regimen of Escitalopram Oxalate, Clonazepam and Trihexyphenidyl, resulting in decreased involuntary tremor during ambulation. The effect of botulinum toxin on cervical dystonia had persisted for more than two years until a relapse occurred at age 24. She presented with episodes of sudden and repetitive twisting movements of her neck to the left and backwards, as well as paroxysmal tilting of the neck to the right, accompanied by head tremor, neck pain and a slight shrug of the left shoulder (Video 1).

Annals of Clinical and Medical Case Reports

Video 1: Patient with Deafness-Dystonia Syndrome caused by ACTB gene mutation presented with generalized dystonia(cervical dystonia, laryngeal dystoniaand dystonic tremor in the extremities and trunk). Cervical dystonia was specifically characterized by episodes of sudden and repetitive twisting movements of her neck to the left and backwards, as well as paroxysmaltilting of the neck to the right, accompanied by head tremor, neck pain and a slight shrug of the left shoulder.

After administration of 200 U of botulinum toxin, consisting of 100 U for bilateral semispinalis capitis, 60 U for the right sternocleidomastoid and 40 U for the left sternocleidomastoid in July 2023, she experienced a comparable positive response within one week, evident through her normal head position and a significant decrease in neck tilt and twist. This improvement has persisted for over six months (Video 2). After the injection of botulinum toxin, her Toronto Western Spasmodic Torticollis Rating Scale score (TWSTRS) significantly reduced from 59 to 29, reflecting a remarkable improvement of 66.1% in her cervical dystonia.

Video 2: Cervical dystonia was alleviated following botulinum toxin injections, as indicated by normal head position and a significant decrease in neck tilt and twist.

5. Discussion

ACTB gene encodes a crucial component of cytoskeleton called β-actin, which involved in diverse functions. Actin can rapidly polymerize from globular subunits into polarized filaments, thereby performing a critical role in diverse functions ranging from whole-cell migration to the movements of subcellular components, such as muscle contraction, subtle movements of neuronal processes, fast motility of immune cells, transport of nutrients, conversion of energy and transmission of signals [5]. In addition, it's involved in cell division and differentiation. ACTB gene mutation could lead to dysfunction of the system which regulate turnover of actin filaments, resulting in an accumulation of actin and its regulatory proteins actin depolymerizing factor/cofilin in the striatum, globus pallidus and substantia nigra, which frequently causes severe infant-onset deafness and juvenile or young-adulthood-onset dystonia [6]. The clinical manifestations of DDS with ACTB gene mutation are heterogeneous, typically including varying degrees of facial dysmorphism, developmental delay, and neurodevelopmental deficits. Some patients also suffered from skeletal abnormalities, visual impairment, focal epilepsy, depression or psychotic episodes, etc [7]. One patient exhibited abnormalities in the bilateral caudate nuclei and basal ganglia on the brain MRI [8]. Brain imaging data indicated that striatal or putaminal neurons and structures containing D2-receptors may be dysfunctional or degenerated [9]. Studies have shown that globus pallidus deep brain stimulation (GPi-DBS) can ameliorate dystonia symptoms to a certain degree, potentially related to structural abnormalities in brain regions such as basal ganglia and striatum as observed through neuroimaging [4,7,9,10].

To date, only 11 cases of DDS with mutation in the ACTB gene c.547C>T, p. (Arg183Trp) have been reported. Due to the rarity of this disease, our report could further expand the phenotype, containing short stature, flattened zygomatic region, and small pointed chin. In addition, compared to other patients who either experienced limited or only partial improvement with botulinum toxin injections, as shown in Table 2 [6,10-13], our patient achieved significant efficacy in the treatment of cervical dystonia, making it a valuable reference for this condition. It is widely acknowledged that botulinum toxin type A is recommended as the first-line treatment for cervical dystonia [14]. Botulinum toxin can effectively block exocytosis at peripheral cholinergic sites including neuromuscular junctions, leading to temporary muscle relaxation through paralysis, ultimately alleviating involuntary movements and correcting postural abnormalities [15]. Besides, cervical dystonia-related pain could be alleviated continuously following repeated injections of IncobotulinumtoxinA [14]. Our patient who presented with paroxysmal twisting of the neck and accompanying pain experienced an improvement in neck posture and relief from associated pain after receiving injections of botulinum toxin into the targeted muscles. The previous patients' inadequate response to treatment with botulinum toxin injections might be attributed to the following reasons. The range of their involuntary movements was extensive, exhibiting either generalized or multifocal dystonia. The local symptoms were severe and complicated, thus neither the standard dose nor even the recommended maximum dose was sufficient in their management [16]. Additionally, inappropriate muscle targeting could result in sub-optimal treatment responses or outright failure [17]. Moreover, as the dystonia was not limited to focal areas but instead generalized, focal botulinum toxin injections yielded limited effectiveness or caused a subjective sense of ineffectuality.

Thus far, three patients have died, two of whom died of aspiration pneu-

monia secondary to dystonia in their twenties and one of whom died of complications of the worsening and uncontrolled dystonia in his late teens [8,18]. Hence, discovering an efficient treatment is of utmost importance. It was reported that 5 patients with GPi-DBS received clinical improvement [4,7,9,10]. However, a patient developed parkinsonism 4 years after GPi-DBS, with imaging evidence displaying signs of degenerating striatal neurons [9]. Another patient underwent the surgery at age 35, and 3 years later she experienced progressive lower-body parkinsonism, associated with unresponsive to levodopa or prolonged GPi-DBS switching-off [7]. Therefore, we recommend considering individual injections of botulinum toxin as a conservative treatment option for managing focal dystonia in patients with DDS.

Table 2: The efficacy of botulinum toxin treatment on patients diagnosed with Deafness-Dystonia Syndrome

Cases	Patients	Clinical manifestations of dystonia	Injection sites	Effects
Gearing M, et al. (2002)[6]	Twins brothers	Severe painful generalized dystonia: 1. Leg dystonia 2. Oculogyric and opisthotonic crises 3. Cranial and bulbar dystonia (spontaneous grimacing, dysarthria, forceful tongue protrusion and dysphagia) 4. Hand and arm dystonia	Focal injections	Not mentioned
Havránková P, et al. (2009)[11]	Male	Severe generalized dystonia: 1. Cervical dystonia 2. Medication-refractory dystonia (bulbar, truncal and limb dystonia)	Neck muscles	Repeated local injections received only partial relief.
Eggink H, et al. (2017)[10]	Female	Severe generalized dystonia: 1. Writer's cramp 2. Cervical dystonia 3. Other dystonia symptoms were not specifically described.	Neck muscles	Focal injections received limited effect without deep brain stimulation. Pallidal stimulation with continuation of botulinum toxin injections led to a substantial improvement.
Freitas JL, et al. (2019)[12]	Female	Severe generalized dystonia: 1. Left lower-limb dystonia 2. Dystonia with dystonic tremor in her upper limbs, dystonic gait	Not mentioned	Botulinum toxin was tried for three times, but was ineffective.
Zavala L, et al. (2021) [13]	Female	Severe multifocal dystonia: 1. Writer's cramp 2. Blepharospasm 3. Prominent cervical dystonia (retrocollis and left head rotation)	Muscles of the eyes	Limited benefit
Our case (2023)	Female	Generalized dystonia: 1. Cervical dystonia 2. Laryngeal dystonia 3. Dystonic tremor in the extremities and trunk	Neck muscles	Cervical dystonia achieved significant improvement.

6. Conclusion

In conclusion, we expand the phenotypic spectrum of DDS with ACTB gene mutation and demonstrate the effectiveness of botulinum toxin injections for the disease. The treatment of botulinum toxin injections should be considered as a conservative treatment for DDS patients with focal dystonia, such as cervical dystonia.

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