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Short Communications

ACTB-associated dystonia-deafness syndrome with good response to DBS GPi revisited

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ABSTRACT

Introduction: Dystonia-deafness syndrome is a rare disorder characterized by dystonia with sensorineural hearing impairment. While various genetic causes have been identified, many cases remain unexplained. Deep brain stimulation of the globus pallidus internus is an established treatment for dystonia, but outcomes vary depending on the underlying cause.

Methods: We conducted a long-term follow-up of a 31-year-old male diagnosed with DDS, initially reported in 2016.

Results: The patient exhibited progressive generalized dystonia and sensorineural hearing loss. At the age of 19, bilateral DBS-GPi implantation was performed, resulting in sustained symptom improvement until the age of 25. However, progressive worsening of dystonia led to the initiation of adjunctive botulinum toxin therapy, which initially provided symptom relief. At the age of 26, disruption of a DBS extension wire caused acute symptom exacerbation, necessitating surgical replacement. Further clinical deterioration was exacerbated by a hardware-related infection, leading to surgical removal of the left DBS system at the age of 30, which prompted placement of a percutaneous endoscopic gastrostomy. At the age of 31, the right-sided DBS system was also removed. Bilateral reimplantation of the DBS-GPi system was performed at the age of 31. Trio exome sequencing identified a *de novo* heterozygous pathogenic *ACTB* variant, p.Arg183Trp.

Conclusion: This case highlights both the benefits and limitations of DBS in *ACTB*-associated dystonia. While this mutation may predict DBS efficacy, long-term outcomes are influenced by disease progression, hardware complications, and systemic factors. Further research is needed to establish *ACTB* variants as predictive markers for DBS responsiveness.

1. Introduction

Dystonia-deafness syndrome (DDS) is a heterogeneous disorder characterized by occurrence of sensorineural hearing loss and dystonia. While it can result from various genetic conditions such as Mohr-Tranebjaerg syndrome (MTS), its cause remains unknown in most cases [1]. Ongoing progress in genetics in recent years has led to the identification of additional genetic causes. Among the identified genes, *ACTB* (MIM * 102630) have been associated with autosomal dominant Baraitser-Winter syndrome 1 (BWS; MIM # 243310) and Dystonia-deafness syndrome 1 (MIM # 607371) characterized by developmental abnormalities, dysmorphic features, sensorineural deafness,

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intellectual disability, and movement disorders such as dystonia [2]. Although initially described as distinct clinical entities, these syndromes are now understood to represent a spectrum of manifestations resulting from mutations in the *ACTB* gene. Understanding the genetic basis of DDS is crucial for accurate prognosis and personalized treatment strategies. While deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an established treatment for dystonia [3,4], long-term results can vary depending on underlying genetic and disease-specific factors [5]. This report highlights the long-term efficacy and challenges of this method of treatment in *ACTB* −associated dystonia, as well as the evolving role of genetic testing in refining clinical care and predicting medical outcomes.

2. Methods

We present a long-term follow-up to a case study of a male born in 1994 diagnosed with DDS, initially reported in 2016 [6]. The patient was regularly examined by movement disorder specialists. The assessments included taking the patient's medical history in the presence of his mother, a general medical examination, a neurological examination, a check and adjustments of the DBS system, Burke-Mardsen-Fahn Dystonia Rating Scale (BMFDRS) assessments, and additional tests performed based on clinical indications. For identification of probable genetic cause trio exome sequencing was performed in 2024. The collected data are part of routine history taking and did not include any additional interventions nor influence medical decisions, therefore the Bioethical Committee approval was not required. Written informed consent was obtained from the patient and documented for the publication of this case and accompanying video materials.

3. Results

The patient initially exhibited bilateral sensorineural hearing loss from the age of 3. Nine years later he presented progressive segmental craniocervical dystonia with jaw-opening, tongue protrusion, retrocollis and gradual overflow including upper limbs. At the age of 17, the patient developed generalized dystonia with continuous movements at risk of status dystonicus. As oral pharmacotherapy with biperiden (6 mg), levodopa with benserazide (62.5 mg), and baclofen (25 mg) tid, was ineffective (BFMDRS = 75), implantation of bilateral DBS-GPi (SJM Brio) was performed at the age of 19, resulting in significant symptom improvement (BFMDRS = 10). Initial targeted genetic testing for *DYT-TOR1A*, *DYT-THAP1,* and *TIMM8A* mutations showed negative results.

The patient reported sustained improvement up to the age of 25. However, in the following months, progressive worsening of jaw opening and tongue dystonia and sagittal anterior shift in cervical dystonia (Video 1 Segment 1 with BFMDRS = 27) necessitated the introduction of botulinum toxin as an adjunctive treatment. OnabotulinumtoxinA (onaBoNT-A) injections were administered: bilaterally to the lateral pterygoid muscles (2 × 25 units), digastric muscles (2x10 units) for jaw-opening dystonia, and to the genioglossus muscle (2 × 15 units) for tongue protrusion. For excessive drooling injections were administered to the parotid glands (2x10 units) and the submandibular glands (2x10 units). For cervical dystonia with sagittal anterior shift (new pattern, previously retrocollis), injections were given to the both semispinalis capitis (2 × 20 units), the sternocleidomastoid muscles (2 × 30 units), and the left levator scapulae (20 units), 260 units in total. The treatment resulted in moderate and marked improvement of cervical and oromandibular (with decrease of drooling) dystonia respectively (Video 1 Segment 2 with BFMDRS = 12). However, repeated dystonic cervical movements caused the lead fracture by imposing mechanical stress on the right DBS extension wire, which led to its disruption and an acute exacerbation of dystonia at the age of 26 (Video 1 Segment 3, BFMDRS = 52), improving after urgent neurosurgical replacement.

Between the ages of 27 and 29, we observed stabilization of dystonia on bilateral GPi-DBS and adjunctive onaBoNT-A therapy. (Video 1 Segment 4, BFMDRS = 13). The monopolar pallidal stimulation parameters were set to set to the amplitude of 4,2–4,7 mA on the right and 4,2–4,8 mA on the left side, with a 130 Hz frequency and 225 μs pulse width bilaterally. Later on, despite continued regular onaBoNT-A therapy and gradually adjusted settings of DBS, dystonia gradually worsened. The symptoms were accompanied by progressive weight loss. Patient refused the PEG placement. At that time, the pharmacotherapy regimen included oral baclofen (25 mg) and biperiden (2 mg) tid.

By the age of 30, he developed skin erosion over the DBS hardware, most likely related to malnutrition, which caused thinning and fragility of the skin and thereby increased mechanical stress over the implanted components, leading to infection and necessitating the removal of the entire left DBS system, while stimulation on the right remained active. Prior to neurosurgical intervention, the monopolar stimulation parameters were set at amplitudes of 4.75 and 4.85 mA for the right and left electrodes, respectively, with a 130 Hz frequency and 225 μs pulse width on both sides. After the surgery, the patient experienced a pronounced worsening of dystonia, along with dysphagia, ultimately leading to cachexia. As a result, his weight dropped from 49 kg at the age of 26 to 37 kg four years later. This deterioration prompted the patient to ultimately consent to PEG placement.

At the age of 31, hardware infection on the right side appeared and resulted in complete removal of the DBS system, followed by severe exacerbation of dystonia (Video 1 Segment 5, BFMDRS = 84). As the response of dystonia to oral drugs was limited, onaBoNT-A therapy of the craniocervical muscles and salivatory glands (for excessive drooling) was continued. Targeted antibiotic therapy and infected teeth extraction were performed. Following successful treatment of the infection, bilateral reimplantation of the DBS-GPi (Abbott Liberta RC) system was performed at the age of 31 in May 2025 without complications and the monopolar stimulation parameters were initially set to the amplitude of 3.5 mA (2.8–4.0), with a 130 Hz frequency and 90 μs pulse width on both sides with mild improvement observed after three months (Video 2, BFMDRS = 40).

Expanded genetic testing using trio exome sequencing performed in 2024 identified a *de novo* heterozygous missense variant in *ACTB*: NM_001101.5: c.547C > T (p.Arg183Trp) − a recurrent variant associated with DDS 1 listed as "pathogenic" in the ClinVar database.

4. Discussion

The presented case shows the longitudinal evolution of DDS in patient who initially markedly improved after DBS-GPi despite the unknown (possibly genetic) cause at the time of first publication in 2016 [6]. We observed the gradual evolution of symptoms from childhood-onset hearing loss and segmental craniocervical dystonia to generalized dystonia, followed by progressive complications including weight loss, infections, and hardware-related problems. Long-term symptom control appears to be relatively modest when compared to established DBS-responsive forms such as DYT-TOR1A dystonia. However, the clear clinical deterioration following hardware complications and device removal underscores the central role of DBS in maintaining motor stability. Adjunctive to DBS therapy with onaBoNT-A improved his quality of life for several years.

Recent genetic testing revealed *ACTB* mutation in our patient. The gene encodes cytoplasmic β-actin, and its genetic alterations are linked to autosomal dominant BWS and DDS 1 [2]. In several published cases, the recurrent p.Arg183Trp variant has been linked to the DDS phenotype. They include a case from the United States describing a male [7] and another from Brazil describing a female [8], both with unremarkable family medical histories, as well as an Argentinian family with affected members [9]. However, none of the aforementioned reports included DBS treatment. Therefore, our case report was revisited to show that symptoms related to this specific mutation may respond to DBS and this treatment option should be offered to such patients.

Our findings align with four previous reports from India [10], the

Netherlands [11], Norway [12], and Italy [13], comprising a total of five patients with marked improvement after DBS implantation, emphasizing its efficacy in patients with dystonia with *ACTB* p.Arg183Trp variant. Coenen et al. [14] highlighted a good response to pallidal stimulation with bilateral cochlear implants in patient with DDS diagnosed with MTS, however genetic background was not confirmed. On the other hand, Beaulieu-Boire et al. [15] reported modest efficacy of DBS for alleviating dystonia in the spectrum of rare inherited disorders as ataxia-telangiectasia and chorea-acanthocytosis. However, within the cohort, the patient diagnosed with Woodhouse-Sakati syndrome, often associated with DDS [1], experienced a significant long-term improvement of 42 % on the BFMDRS. Brüggemann et al. [16] and Artusi et al. [17] also highlighted that specific genetic backgrounds of dystonia may correlate with pallidal stimulation responsiveness, while others may not, further supporting the hypothesis that *ACTB* mutations could serve as a predictive marker for favorable DBS-GPi outcomes. At the same time, our case illustrates the challenges of long-term management of inherited dystonia. Complications such as hardware infection and eventual removal of the system repeatedly led to marked worsening of dystonia what proves that DBS is a really effective treatment. OnaBoNT-A therapy proved to be an important adjunctive treatment, providing symptomatic relief of jaw-opening, tongue protrusion, and cervical dystonia, particularly when DBS efficacy was interrupted. However, in dystonia with a degenerative component, such as X-linked dystonia-parkinsonism due to *TAF1* mutations, long-term outcomes are determined not only by treatment-related factors but also by disease progression. In such cases, an initially favorable response to DBS may gradually wane as the underlying pathology advances, underscoring the importance of careful preoperative counseling to manage patient expectations.

This revisited case highlights both the potential and the limitations of DBS-GPi in inherited dystonia, underscoring the challenges of long-term follow-up. It also emphasizes the importance of considering genetic retesting given the continuous advancement of genetic technologies and the identification of new dystonia-associated genes. Our findings suggest that dystonia caused by *ACTB* mutations may respond well to bilateral pallidal stimulation, nevertheless further studies are needed to confirm this observation.

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CRediT authorship contribution statement

Jakub Kasprzak: Data curation, Investigation, Writing – original draft. **Jarosław Dulski:** Data curation, Investigation, Writing – review & editing. **Michał Schinwelski:** Data curation, Investigation, Writing – review & editing. **Magdalena Krygier:** Investigation, Writing – review & editing. **Michael Zech:** Funding acquisition, Investigation, Writing – review & editing. **Jarosław Sławek:** Supervision, Validation, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100406.

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