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Case Reports

Bi-pallidal deep brain stimulation as an effective therapy in atypical two-stage evolution adult-onset *KMT2B*-related dystonia

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ABSTRACT

We report an adult-onset KMT2B-related dystonia with a two-stage evolution: focal cervical onset followed by rapid generalization. Whole genome sequencing identified a likely pathogenic KMT2B variant. Bi-pallidal deep brain stimulation led to an 83% motor improvement, highlighting its therapeutic potential in late-onset atypical two-stage evolution KMT2B-dystonia.

Monoallelic variants in *KMT2B* (lysine-specific methyltransferase 2B) are recognized cause of early-onset dystonia (DYT-*KMT2B*) (OMIM ID: 606834) [1]. Typically, onset occurs in childhood, within the first decade, initially as focal lower-limb dystonia, later generalizing with cranio-cervical and bulbar involvement [1]. More complex phenotype occurs in 30-50% of cases [1]. Dystonia impairment is broad ranging from mild-to-moderate to dependence. Late-onset presentations are rare, with only 20 reported patients (mean onset: 34 years) [2–4], often presenting as focal dystonia (70%), while others exhibit additional features (30%) [2–4].

Meta-analysis has demonstrated the efficacy and safety of bi-pallidal deep brain stimulation (GPi-DBS) in early-onset DYT-*KMT2B* [5], but data on late-onset cases remain limited.

We describe an atypical two-stage course with dramatic improvement following GPi-DBS in an adult-onset DYT-*KTM2B* patient.

A woman developed progressive isolated cervical dystonia with left torticollis and laterocollis from the age of 33. She had no personal or family medical history, nor prior exposure to dopamine receptor antagonists. Birth delivery, and psychomotor development were normal. Initially, she was treated by annual botulinum toxin A (BTA) injections with very good results.

At age 47, she progressively developed blepharospasm successfully treated by BTA injections. Two years later, the dystonia significantly worsened manifesting a cranio-caudal progression with oromandibular dystonia and cranio-cervical jerks (Video 1). These symptoms did not improve with BTA injections.

At 50, symptoms extended to the upper limbs and trunk, evolving into generalized myoclonic dystonia (Video 1). Severe oromandibular involvement led to chewing/swallowing difficulties and 25 kg weight loss within three months, necessitating gastrostomy. Burke-Fahn-Marsden Movement and Disability Subscales (BFMMS/BFMDS) scores were 30/21 respectively, with no response to trihexyphenidyl, benzodiazepines, levodopa, or tetrabenazine.

Extensive investigations (brain MRI, metabolic/infectious workup, antineuronal antibodies, CSF analysis, PET scans) were unremarkable. Whole genome sequencing revealed a c.631T>G/p.(Cys211Gly) (NM_014727.2) monoallelic variant in *KMT2B*. This variant was absent in the gnomAD_v3 database, involved a highly conserved nucleotide (PhastCons 0.99), and was predicted to enhance a cryptic splicing site in the exon 2 leading to an abnormal transcript (splice AI donor gain score 0.36; SPIP: creation of a new splice site risk 43.04%; MaxEntScan 5'ss score +90.85). Because of these characteristics and the phenotype of the patient, we considered this variant as likely pathogenic.

Due to rapid worsening and treatment resistance, GPi-DBS was performed. Postoperative dystonic crisis required intensive care and midazolam/clonazepam. At two months, BFMMS/BFMDS scores reduced to 5/1 (Video 1). Stimulation parameters were 3.2 mA, 210 μs, 130 Hz bilaterally. Oral feeding resumed, weight improved, and medication was discontinued. Only blepharospasm persisted, well controlled with BTA.

We present a novel case of adult-onset DYT-*KMT2B* associated with a

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likely pathogenic variant, highlighting three key aspects: (i) an atypical two-phase clinical progression, (ii) a remarkable response to bilateral pallidal deep brain stimulation (GPi-DBS), and (iii) genetic findings that expands the phenotypic spectrum.

Late-onset dystonia due to *KMT2B* variants remains sparsely described (20 cases), typically presenting as cervical dystonia (70%) at a mean age of 34y [2–4]. Our patient followed an unusual biphasic course: initial focal cervical dystonia responsive to BTA, followed by rapid generalization with cranio-caudal spread, severe myoclonus, oro-mandibular dystonia, and substantial weight loss. This pattern had not been previously described, though phenotypic evolution is rarely detailed in reports.

KMT2B encodes a lysine-specific methyltransferase involved in epigenetic regulation [1]. Phenotypes range from asymptomatic carriers to severe early-onset dystonia with intellectual disability [1,2]. The relatively milder presentation and late onset in our patient might suggest that the loss of function is not complete with the identified variant, unlike *KMT2B* protein-truncating variants or microdeletions that confer a more severe phenotype. However, genotype-phenotype correlations in DYT-*KMT2B* remain challenging to establish, as disease severity, progression, and response to treatment appeared to be influenced by multiple factors beyond the mutation type [1].

DBS is well established for early-onset DYT-*KMT2B*, but data on its efficacy in late-onset cases remain limited [5]. In our patient, GPi-DBS resulted in a dramatic clinical response, with an 83.33% reduction in the BFMMS score and a 95.24% improvement in the BFMDS score within two months postoperatively. This intervention allowed the resumption of oral feeding and the discontinuation of prior ineffective medical therapies. While previous studies demonstrate robust outcomes in early-onset cases [2], our findings provide compelling evidence supporting its usefulness in adult-onset cases, even after a prolonged disease course. The rapid improvement observed post-DBS in this patient aligns with previous reports of significant motor and functional recovery in DYT-*KMT2B* [5] and underscores the value of DBS as a first-line treatment option for severe and/or refractory dystonia.

In conclusion, this case expands the phenotypic spectrum of adult-onset DYT-*KMT2B*, illustrating an atypical biphasic progression and reinforcing GPi-DBS as a highly effective treatment. Identifying novel *KMT2B* variants remains essential for refining genotype-phenotype correlations and optimizing management strategies. Early recognition and timely DBS intervention could significantly improve outcomes in similar cases.

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CRediT authorship contribution statement

Georges-Junior Kahwagi: Data curation, Writing – original draft. **Cécile Hubsch:** Conceptualization, Data curation, Writing – review & editing. **Lydie Burglen:** Data curation, Writing – review & editing. **Jean-Philippe Brandel:** Writing – review & editing. **Sophie Sangla:** Conceptualization, Data curation, Writing – review & editing. **Clément Desjardins:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical compliance statement

The patient gave her written inform consent. Verbal and written informed consent were obtained from the subject. The authors confirm that the approval of an institutional review board was not required for this work. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2025.100314.

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