

Deep Brain Stimulation in Dystonia: Disentangling Heterogeneity

Alberto Albanese, MD* 

Dystonia syndromes have many different causes (inherited, acquired, or idiopathic) and variable phenomenology, as dystonia can be isolated, combined with another movement disorder or with additional neurological features.¹ Symptomatic treatment is based on oral medications, focal injections of botulinum neurotoxins (BoNT), or deep brain stimulation (DBS).² In this issue of *Movement Disorders Clinical Practice*, 2 patients with inherited combined syndromes are independently described to benefit from DBS targeted to the globus pallidus internus (GPi). One patient had mutations in the *SERAC1* gene causing an autosomal recessive nuclear mitochondriopathy³; the other carried a pathogenic mutation in the *ADCY5* gene causing a dystonic/dyskinetic storm.⁴ Follow-up assessments confirmed that both patients had a substantial improvement of dystonia and a less evident response of chorea. These 2 cases add to a growing list of evidence on the efficacy of GPi DBS in dystonia.

The possibility of using GPi DBS was first shown in patients with early-onset generalized inherited dystonia, specifically *TOR1A* (DYT1) gene mutation carriers,⁵ who are now known to have long-lasting benefit.⁶ GPi DBS is currently accepted as a first-line symptomatic indication for DYT1 dystonia. Observations of patients with other isolated or combined inherited dystonia syndromes have shown variable evidence of efficacy. A recent meta-analysis indicated that only DYT1 mutation carriers benefit in both functional and motor improvements following GPi DBS.⁷ *THAP1* (DYT6) and *PANK2* (PKAN) gene mutation carriers instead have significant motor but little functional improvement. Patients with inherited combined dystonia caused by *SGCE* (DYT10) gene mutations were also reported to significantly improve following GPi DBS not only in dystonia but also in myoclonus and overall functioning.⁸ Data on patient functioning after DBS implant are not available in all cases. Moderate improvements have been observed instead in patients with *TAF1* (DYT3) or *ANO3* (DYT24) gene mutations.^{9,10} Finally, it has also become evident that patients with mutations in the *ATP1A3* gene (DYT12) do not improve at all, either after GPi DBS or pallidotomy.^{11,12} It has become clear that outcomes vary across

inherited dystonia syndromes and that *ATP1A3* mutation carriers remain a so far unique example of nonresponse to GPi DBS. In patients carrying mutations in this gene there is indication not to perform pallidal surgery for dystonia.

Acquired dystonia syndromes can also improve with GPi DBS. The most impressive outcomes have been reported in patients with tardive dystonia, where motor features and disability have been reported to reach an 85% improvement.^{13–15} In patients with dystonic cerebral palsy, instead, there is a significant variability of outcomes, with a maximum improvement abutting 49%.¹⁶ Figure 1 provides a summary view of the average reported improvements in inherited and acquired dystonia syndromes following GPi DBS.

Dyskinetic storm (or status dystonicus) is a rare, potentially life-threatening movement disorder characterized by the development of increasingly frequent or continuous severe episodes of generalized dystonic spasms that require emergency in-hospital management.¹⁷ The term *dyskinetic* indicates that these patients may have a combination of dystonia, chorea, and other involuntary movements. Few years after the introduction of GPi DBS for DYT1 dystonia, the same approach has been used in patients with severe generalized inherited dystonia syndromes who had developed dystonic/dyskinetic storms.¹⁸ GPi DBS has proven efficacious and has become a first-line approach in patients with dyskinetic/dystonic storms of different etiologies, such as ceroid lipofuscinosis, *GCH1* or *PANK2* mutations, methylmalonic acidemia, cerebral palsy, *N*-methyl-D-aspartate receptor encephalitis, and so on. In these cases, assessment of outcome is not based on dystonia rating scales but, rather, on the number and duration of dyskinetic spells at baseline and after implant.⁴ These data are therefore difficult to compare with those collected in patients with other dystonia syndromes. Furthermore, most reports on dyskinetic/dystonic storms are single cases or small series that are difficult to arrange into a coherent set to compare different indications. Overall, GPi DBS is convincingly efficacious and considered to provide a treatment solution to this medical emergency. Continuing observations are needed, however, as it has been

¹Department of Neurology, IRCCS Humanitas Research Hospital, Milan, Italy; ²Department of Neuroscience, Catholic University, Milan, Italy

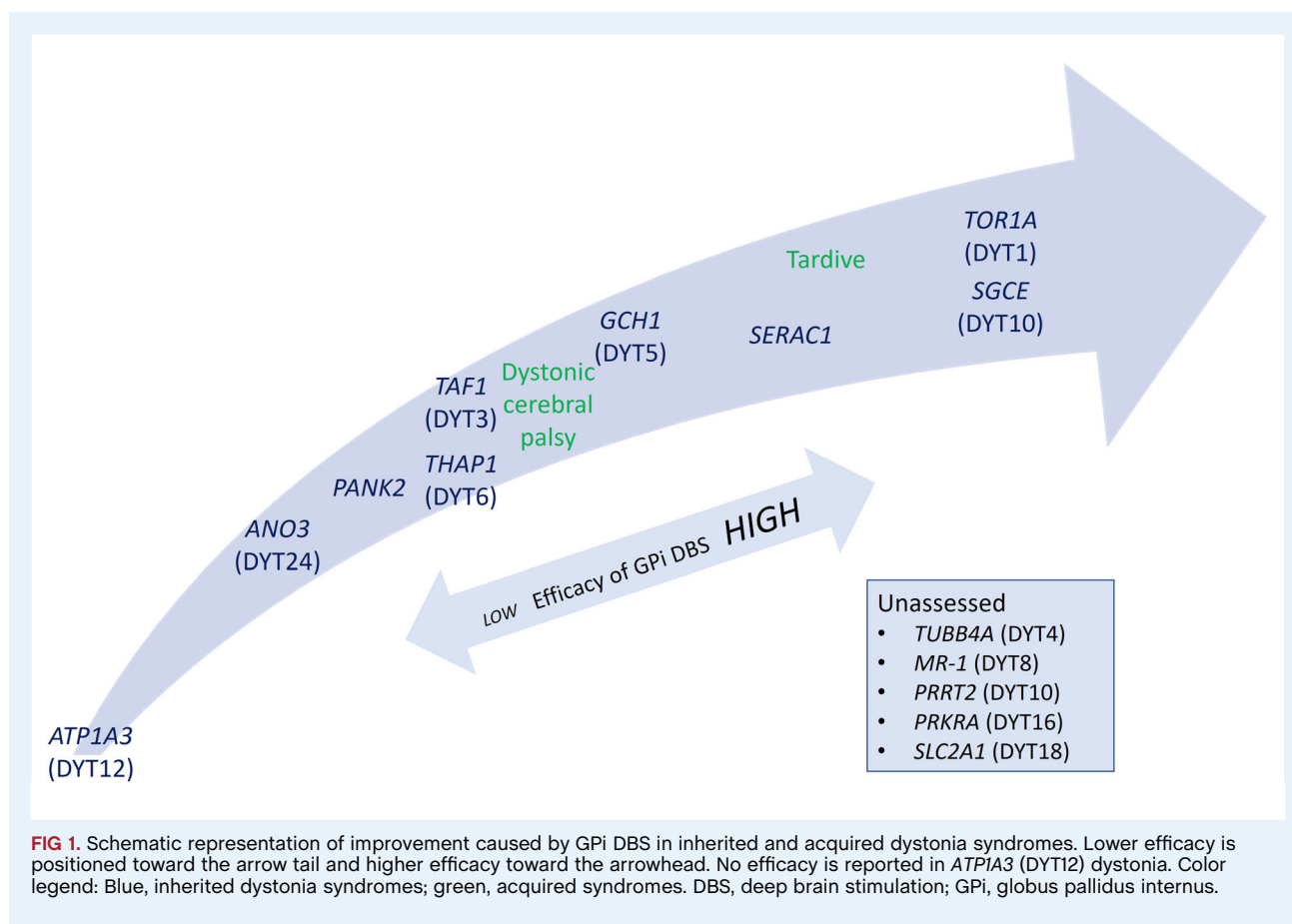
*Correspondence to: Dr. Alberto Albanese, Department of Neurology, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy; E-mail: alberto.albanese@unicatt.it

Keywords: dystonia, deep brain stimulation.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 13 October 2020; accepted 24 October 2020.

Published online 00 Month 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13113



shown that dyskinetic storms can still occur in patients with a functioning GPi DBS implant.¹⁹

DBS was originally restricted to severe cases of dystonia, usually with early onset and a defined etiology. Recently, this treatment option was extended to idiopathic focal or segmental cases that usually have adult onset. Cervical dystonia is the most common form of adult-onset idiopathic focal or segmental dystonia. The first-line treatment here is BoNT; GPi DBS provides a second-line offering.² A short double-blind sham-controlled trial first demonstrated efficacy of GPi DBS in cervical dystonia patients who had discontinued BoNT treatment.²⁰ Efficacy of GPi DBS was also reported in patients with segmental cranial dystonia (Meige syndrome)²¹ and in other adult-onset idiopathic dystonias. Overall, these data were considered of insufficient quality by a recent Cochrane review,²² and new higher quality publications are warranted.

Knowledge on the indications for GPi DBS in dystonia syndromes is expanding, and a significant new source of information is provided by reports on single rare dystonia syndromes, such as *SERAC1* and *ADCY5* mutations in this issue.^{3,4} This scattered information needs to be assembled into consistent and comprehensive knowledge that will clarify specific indications and predictors of outcome for the variety of dystonia syndromes.

Disclosures

Ethical Compliance Statement: Patient consent and the review of an institutional review board were not required for this work. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: No funding was received for this work. The author has no conflicts of interest to report.

Financial Disclosures for Previous 12 Months: There are no financial disclosures to report. ■

References

- Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28(7):863–873.
- Albanese A, Di Giovanni M, Lalli S. Dystonia: diagnosis and management. *Eur J Neurol* 2019;26(1):5–17.
- Sharma VD, Bueteifisch CM, Kendall FD, Gross RE, DeLong MR, Juncos JL. Secondary dystonia in a novel mitochondriopathy responsive to deep brain stimulation therapy. *Mov Disord Clin Pract* 2020 Aug 24;7. <https://doi.org/10.1002/mdc3.13075> [Epub ahead of print].
- Eisenberg HJ, Malinova V, Mielke D, Bähr M, Görcke MB, Riesen C. *ADCY5*-induced dyskinetic storm rescued with pallidal deep brain

- stimulation in a 46-year-old man. *Mov Disord Clin Pract* 2020 Aug 24;7. <https://doi.org/10.1002/mdc3.13076> [Epub ahead of print].
5. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B. Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. *Lancet* 2000;355(9222):2220–2221.
 6. Cif L, Vasques X, Gonzalez V, et al. Long-term follow-up of DYT1 dystonia patients treated by deep brain stimulation: an open-label study. *Mov Disord* 2010;25(3):289–299.
 7. Artusi CA, Dwivedi A, Romagnolo A, et al. Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2020;91(4):426–433.
 8. Kosutzka Z, Tisch S, Bonnet C, et al. Long-term GPi-DBS improves motor features in myoclonus-dystonia and enhances social adjustment. *Mov Disord* 2019;34(1):87–94.
 9. Abejero JEE, Jamora RDG, Vesagas TS, et al. Long-term outcomes of pallidal deep brain stimulation in X-linked dystonia parkinsonism (XDP): up to 84 months follow-up and review of literature. *Parkinsonism Relat Disord* 2019;60:81–86.
 10. Yoo D, Kim HJ, Chae JH, Paek SH, Jeon B. Successful Pallidal deep brain stimulation in a patient with childhood-onset generalized dystonia with ANO3 mutation. *J Mov Disord* 2019;12(3):190–191.
 11. Albanese A, Di Giovanni M, Amami P, Lalli S. Failure of pallidal deep brain stimulation in DYT12-ATP1A3 dystonia. *Parkinsonism Relat Disord* 2017;45:99–100.
 12. Brucke C, Horn A, Huppke P, Kupsch A, Schneider GH, Kuhn AA. Failure of Pallidal deep brain stimulation in a case of rapid-onset dystonia parkinsonism (DYT12). *Mov Disord Clin Pract* 2015;2(1):76–78.
 13. Franzini A, Marras C, Feroli P, Zorzi G, Bugiani O, Romito L, Broggi G. Long-term high-frequency bilateral pallidal stimulation for neuroleptic-induced tardive dystonia. Report of two cases. *J Neurosurg* 2005;102(4):721–725.
 14. Sako W, Goto S, Shimazu H, et al. Bilateral deep brain stimulation of the globus pallidus internus in tardive dystonia. *Mov Disord* 2008;23(13):1929–1931.
 15. Sanger TD. Childhood onset generalised dystonia can be modelled by increased gain in the indirect basal ganglia pathway. *J Neurol Neurosurg Psychiatry* 2003;74(11):1509–1515.
 16. Elia AE, Bagella CF, Ferre F, Zorzi G, Calandrella D, Romito LM. Deep brain stimulation for dystonia due to cerebral palsy: a review. *Eur J Paediatr Neurol* 2018;22(2):308–315.
 17. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. *Brain* 1998;121(Pt 2):243–252.
 18. Zorzi G, Marras C, Nardocci N, et al. Stimulation of the globus pallidus internus for childhood-onset dystonia. *Mov Disord* 2005;20(9):1194–1200.
 19. Nerrant E, Gonzalez V, Milesi C, et al. Deep brain stimulation treated dystonia-trajectory via status dystonicus. *Mov Disord* 2018;33(7):1168–1173.
 20. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol* 2014;13(9):875–884.
 21. Wang X, Zhang Z, Mao Z, Yu X. Deep brain stimulation for Meige syndrome: a meta-analysis with individual patient data. *J Neurol* 2019;266(11):2646–2656.
 22. Rodrigues FB, Duarte GS, Prescott D, Ferreira J, Costa J. Deep brain stimulation for dystonia. *Cochrane Database Syst Rev* 2019;1:CD012405.