

Deep brain stimulation for cervical dystonia

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Dystonia is a movement disorder characterised by sustained or intermittent muscle contractions that cause abnormal, often repetitive, movements, postures, or both. The severity and phenomenology of dystonia vary widely and various causes have been identified.¹ Treatment with deep brain stimulation (DBS) of the globus pallidus internus (GPi) was first announced 14 years ago for patients with inherited isolated DYT1 (also known as TOR1A) dystonia.² Since then, GPi DBS has been tested successfully on various dystonia syndromes, including isolated or combined presentations and forms with different causes: idiopathic, inherited, or acquired.³ Furthermore, GPi DBS is thought to be a life-saving treatment for status dystonicus, which is a neurological emergency. DBS is thought to improve dystonia because the stimulation desynchronises the excessive synchronised pallidal activity, thus restoring a normal plasticity within the sensorimotor loop,⁴ an effect that takes place gradually and can last for more than 10 years in patients with generalised DYT1 dystonia.

Cervical dystonia is the most common presentation of isolated dystonia, with an estimated prevalence of 28–183 cases per million people,⁵ and botulinum toxin type A treatment is the accepted standard of care.⁶ The success of botulinum toxin treatment is dependent on several variables, including the relative combination of dystonic postures and movements (particularly dystonic tremor), which vary in each patient; the choice of muscles to inject; and the precision of botulinum toxin targeting. Experienced physicians adjust these variables at each subsequent treatment cycle, based on the effects noted after previous injections. An observational study⁷ reported a 40% improvement of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score in patients with cervical dystonia after botulinum toxin treatment, with a similar improvement in efficacy, disability, and pain subscores. Patients with predominant laterocollis, no dystonic tremor, and no concomitant medications responded better to botulinum toxin treatment.

DBS has recently emerged as a treatment option for cervical dystonia. Initial observations showed remarkable improvements with either subthalamic nucleus⁸ or GPi stimulation,⁹ and recent studies have had similar results with stimulation of either target.¹⁰ However, GPi has been the target of choice in most studies of cervical

dystonia. A class III study with long-term follow-up reported a 49% improvement in the total TWSTRS score 1 year after GPi implantation and a 47% improvement at 5 years.¹¹ The severity, pain, and disability subscores improved similarly. Shorter-term observations (≤ 1 year) have shown less improvement compared with longer post-implant follow-ups (≥ 2 years),¹² suggesting that at least 1 year of observation is needed to fully appreciate the effects of GPi DBS on dystonia.

In *The Lancet Neurology*, Jens Volkmann and colleagues¹³ present the results of the first sham-controlled study of GPi DBS in cervical dystonia. The study had a relatively short, 3-month period for post-implant comparison of active and sham stimulations, followed by a further 3 months of open-label surveillance in the active stimulation group, and 6 months of active stimulation for those initially assigned to sham stimulation, to make a total of 6 months of active stimulation in both groups. Remarkably, Volkmann and colleagues¹³ reported a negligible 3% further improvement of the TWSTRS severity subscore at 6 months in the active stimulation group, compared with the initial improvement of 26% at 3 months. Additional benefit might be expected in the long term. These data are not meant to measure the dimension of clinical improvement in patients with cervical dystonia; rather, they provide strong proof of efficacy for GPi DBS in the most common dystonia type. These data will likely lead to changes in neurological practice for cervical dystonia and reposition the indications for DBS and botulinum toxin.

This new study raises more questions than it answers. First, the concept of cervical dystonia refractory to botulinum toxin treatment is intriguing when considered in the context of clinical practice. Non-response to botulinum toxin treatment might result from inappropriate injection schemes, insufficient dosing, wrong muscle selection, and an insufficient number of treatment attempts. The injector's experience is crucial, particularly in complex cases. For this study, experienced handling of patients and at least three botulinum toxin treatment cycles were required before inclusion. Second, patients with cervical dystonia are known to stop botulinum toxin treatment for various reasons, including subjective dissatisfaction

and unwillingness to attend repeated treatment cycles. These patients might prefer a one-off approach such as DBS to repeated botulinum toxin treatment. Third, cervical dystonia has a marked negative effect on patients' quality of life¹⁴ that can be ameliorated by botulinum toxin treatment; the corresponding information for GPi DBS in cervical dystonia is still insufficient for a comparison. Fourth, experience obtained in Parkinson's disease and other movement disorders has shown that DBS is not a last resort in the treatment algorithm: the indication and time for surgery depend on strict selection criteria that include disease cause and phenomenology.¹⁵ A coherent set of such criteria is available for generalised dystonia, but not yet for cervical dystonia. Hints from earlier studies suggest that tremor-dominant cervical dystonia might respond better to GPi DBS, whereas botulinum toxin treatment might be optimal for posture-dominant forms, and that complex forms involving deep neck muscles might be suitable for GPi DBS.

New trials should be designed to provide answers to such questions. For the time being, however, Volkmann and colleagues have shown that GPi DBS is a worthy contender for the treatment of patients with cervical dystonia.

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Anti-CGRP antibodies: a new approach to migraine prevention

In *The Lancet Neurology*, David Dodick and colleagues¹ introduce monoclonal antibodies into the specialty of primary headache therapy. They report findings from a randomised, placebo-controlled, double-blind, phase 2 clinical trial of LY2951742, a neutralising humanised monoclonal antibody against calcitonin gene-related peptide (CGRP), for migraine prevention. The subcutaneous administration of LY2951742 once every 2 weeks reduced the mean number of migraine headache days per 28-day period between baseline and weeks 9–12 (primary endpoint; least-squares mean difference –1.2, 90% CI –1.9 to –0.6; $p=0.0030$) in a population with a high frequency of migraine;

the antibody was also superior to placebo in several secondary endpoints after 12 weeks of treatment. The findings from this study show for the first time that scavenging of CGRP by an antibody is a sufficient mechanism to prevent migraine attacks.

CGRP was brought to the attention of headache researchers and clinicians more than 20 years ago with the finding that concentrations of this peptide were raised in jugular vein blood during acute migraines and cluster headaches.² Ever since, CGRP has been regarded as a key neurotransmitter in acute migraine headaches. Before this hypothesis was established, CGRP had been detected in the central and peripheral nervous system, notably

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