

Bilateral pallidal neurostimulation—long-term motor and cognitive effects in primary generalized dystonia

Original article Vidailhet M *et al.* (2007) Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol* 6: 223–229

SYNOPSIS

KEYWORDS bilateral deep-brain stimulation, cognition, globus pallidus pars interna, motor symptoms, primary generalized dystonia

BACKGROUND

Bilateral pallidal deep-brain neurostimulation (DBS) has been shown to improve motor symptoms and overall quality of life in patients with severe primary generalized dystonia, but the long-term efficacy and safety of this therapy are unknown.

OBJECTIVES

To assess the long-term efficacy of pallidal DBS for the treatment of motor symptoms in generalized dystonia, and to determine whether this therapy adversely affects cognitive performance, mood, and quality of life.

DESIGN AND INTERVENTION

This French, prospective, multicenter study monitored 22 patients (mean age 30 years; range 14–54 years) with primary generalized dystonia (median duration of disease 18.5 years; range 4–37 years) who were treated with pallidal DBS. In 19 patients, both therapeutic electrode contacts were localized in the globus pallidus pars interna (GPi) or the internal medullary lamina; in the other three patients, one of the two active electrode poles was in the globus pallidus pars externa. The stimulation settings were similar throughout the study period. At baseline (before surgery), and at 1 year and 3 years after surgery, an independent expert appraised patient movement and disability using standardized video recordings. Cognitive function, mood and patient quality of life were also assessed at these time points. The study data were analyzed on an intention-to-treat basis.

OUTCOME MEASURES

Outcome measures were movement and disability scores (Burke–Fahn–Marsden dystonia scale), patient quality of life (SF-36), mood (Beck Depression Inventory [BDI]), and cognition (revised Wechsler adult intelligence scale [WAIS-R], mini-mental status examination [MMSE], progressive matrices of Raven PM 38, the Grober and Buschke test, and the Wisconsin card-sorting test [WCST]).

RESULTS

The motor improvement observed at 1 year (51% improvement from baseline) was maintained at 3 years (58% improvement), with significant improvements in the total movement score and the upper and lower limb subscore at 3 years compared with at 1 year. Scores on the BDI, WAIS-R and MMSE were unchanged from baseline at both 1 and 3 years. There were considerable improvements in concept formation and reasoning (Raven PM 38), memory (free recall and total recall of the Grober and Buschke test), and executive functions (WCST total errors) that were maintained at 3 years. A 1-year improvement in overall quality of life was also maintained at 3 years ($P=0.02$, 3 years vs baseline); in particular, general health ($P=0.02$), physical functioning ($P=0.008$), and pain ($P=0.01$) improved relative to preoperative levels. During the study period, the stimulator was removed or switched off bilaterally in two patients because of infection or lack of improvement, and the device was switched off unilaterally in three patients because of unilateral lead fracture or stimulation-related adverse events.

CONCLUSION

Long-term bilateral pallidal DBS continues to improve motor symptoms, memory, and overall quality of life for at least 3 years in patients with primary generalized dystonia, and does not adversely affect mood or cognition.

COMMENTARY

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Primary generalized dystonia is not common, but it mainly affects young people, can be disabling and can have major impacts on quality of life. Most devastating is its unresponsiveness to pharmacological interventions. With the advent of DBS for Parkinson's disease, stimulation of the GPi was observed to eliminate not only levodopa-induced dyskinesia, but also dystonia. GPi DBS was pioneered in 1998 for children severely affected by primary generalized dystonia (bedridden, requiring feeding tubes and respiratory support) as a palliative and experimental procedure.¹ Since then, the short-term benefits for adults with generalized and segmental dystonia have been reported in two well-designed clinical trials.^{2,3} The 3-year follow-up data from the first of these cohorts now confirm that DBS provides sustained benefits.

This study has many important and convincing features, including a prospective multicenter design, a fairly homogenous patient group, 100% follow-up, and standardized video recordings scored by an independent blinded expert. Although double-blinded, controlled studies are ideal, they are impractical (patients usually know when a correctly placed GPi DBS device is turned on or off) and difficult to implement. The most important aspect of the Vidailhet *et al.* study is the intention-to-treat analysis: pallidal DBS improved outcome even with the inclusion of patients in whom stimulation was turned off or electrodes were removed. A 58% improvement in motor control was sustained over the 3-year follow-up period. Quality of life and some neuropsychological measures improved over time. A further notable attribute of this study was that industry had no role in data collection, analysis, interpretation or writing.

No clinical trial is without limitations. In this case, medication changes were not controlled. Five patients had their devices removed or turned off unilaterally or bilaterally because of infection, stimulation-induced adverse effects on speech, or lack of benefit. These complications are similar to those reported for DBS in general; however, some techniques can reduce such occurrences.⁴ An important question is whether these results can be widely generalized. Although patient selection was broad and exclusion criteria standard for

DBS surgery,² each center had highly specialized academic expertise and considerable experience with DBS surgery and programming.

This paper raises several interesting issues. For example, although health-care utilization was documented, no economic analysis was performed to determine cost-effectiveness of DBS for dystonia. Three patients continued to benefit from unilateral DBS, which indicates that the unilateral approach could be sufficient, potentially reducing risks and costs. Unfortunately the information provided about these unilateral successes is minimal. Improvements in cognitive tests are hard to explain in terms of medication changes or learning effects, and deserve further exploration. Finally, the issue of optimum electrode placement remains unresolved. Ninety-five percent of the active electrodes were localized in the GPi or internal medullary lamina, but excellent results also occurred with placement in the globus pallidus pars externa. It remains unclear why the above localizations outside the motor territories of the GPi might be acceptable targets. So even though this study seems to have established surgical therapy as an excellent option, it has also raised new questions that require further experimental work.

For those who treat patients with dystonia, these data confirm and validate observations from individual patients. The original paper of Vidailhet *et al.*² marked the advent of prospective multicenter clinical trials of DBS for movement disorders. The current paper has defined the long-term efficacy of DBS for primary generalized dystonia.

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Competing interests

The author has declared an association with Medtronic. See the article online for full details of the relationship.

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PRACTICE POINT

Bilateral pallidal stimulation provides sustained improvement in motor control and quality of life in patients with primary generalized dystonia