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COMMENTARY

Long-term benefit from deep brain stimulation of the subthalamic nucleus: is it for everyone?

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Abstract

Although deep brain stimulation (DBS) has revolutionized our approach to therapy for patients with advanced Parkinson's disease, many questions remain. Should DBS be instituted earlier in the course of the disease? Why do some patients show striking improvements whereas others show limited benefit even when lead locations appear to be similar? Why can some patients markedly reduce medications whereas others cannot? What is the optimal target site for DBS and how does it work? One question that has long been asked but only recently become addressable is how long the therapeutic effect of DBS can be sustained in the face of what is still a progressive, neurodegenerative disease? A recent article by Castrioto and colleagues, 'Ten-year outcome of subthalamic stimulation in Parkinson disease', seeks to address this question. The authors report significant improvement at 10 years following the onset of subthalamic nucleus DBS in the off UPDRS (Unified Parkinson's Disease Rating Scale) III total motor score, tremor and bradykinesia subscores, UPDRS II meds on and off scores, and UPDRS IV dyskinesia and motor fluctuation score as well as a significant reduction in the levodopa equivalent daily dose when compared with baseline. Does this finally answer our question of the longevity of DBS? I would suggest not. The article by Castrioto and colleagues provides evidence that some patients can expect improvement for 10 years or longer. However, the young age of onset for patients in this study (average of less than 40 years) combined with a substantial loss of patients to follow-up (23 out of 41) likely leads to a data set that was biased in favor of better long-term outcomes, making it unlikely that the data from this study can be applied to the majority of older patients undergoing DBS, who are more likely to follow a more progressive course. Thus, the present findings are encouraging for some but are not likely to be predictive for all or even for most of the patients currently undergoing this procedure. In spite of these problems, one cannot help but be encouraged by the results of a study that was done early in the course of implementing DBS and that shows continued improvement for patients as long as 10 years following implantation.

Deep brain stimulation (DBS) has proven effective in the treatment of patients with advanced Parkinson's disease (PD), turning back the clock for patients and significantly improving their quality of life. The majority of studies of DBS for PD, however, report follow-up times of less than 2 years and many a year or less. A critical question remains: how long will the benefits of DBS for PD last?

A recent article by Castrioto and colleagues, 'Ten-year outcome of subthalamic stimulation in Parkinson disease' [1], addresses this question. This topic is important for those who use DBS to treat patients with PD and is particularly meaningful for patients who are weighing the potential risks and benefits of surgery. The observation that patients who had advanced PD and who underwent subthalamic nucleus (STN) DBS maintained significant motor benefit with reduced anti-parkinsonian medication requirements over the course of a decade is quite remarkable and a testament to the therapy. However, before we generalize these data to all patients undergoing DBS for PD, it is important that we take a hard look at demographic variables and methodological problems associated with this type of study. Although these problems are difficult to overcome, they cannot be ignored.

First, I applaud the authors for their effort. Clinical studies are difficult to do and even harder to do well. Long-term outcome studies are sorely needed but are rarely performed. Many variables have to be taken into account to obtain meaningful data. Getting patients back for scheduled visits, ensuring that the conditions of assessment are meaningful and performed the same way each time, allowing for or taking into account variations in lead location and optimization of stimulation parameters,

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and understanding the nuances of wash-out and wash-in times for DBS and medication effects are just some of the issues that have to be dealt with when doing this type of study [2,3].

The article by Castrioto and colleagues reports significant improvement at 10 years following the onset of STN DBS in the off UPDRS (Unified Parkinson's Disease Rating Scale) III total motor score, tremor and bradykinesia subscores, UPDRS II meds on and off scores, and UPDRS IV dyskinesia and motor fluctuation score as well as a significant reduction in the levodopa equivalent daily dose when compared with baseline. The strengths of the study include the blinded assessments through videotape ratings and the long-term follow-up. The importance of the study is the observation that some patients undergoing STN DBS can maintain motor benefit and improved quality of life up to and perhaps longer than 10 years while reducing anti-parkinsonian medication. Weaknesses include the significant dropout rate and relatively young age of the cohort. Only 18 out of 41 patients were followed for 10 years, and those returning for long-term follow-up likely represent a group biased toward good outcomes. The mean age of those patients completing the long-term follow-up was also considerably younger than that of most patients undergoing this type of surgery. The mean age at surgery in this study was 52.7 years, and the average age at onset was less than 40 years, characterizing the group, on average, as a young-onset age group. Patients with young-onset PD are usually characterized by slower disease progression and show better long-term outcomes compared with older-onset patients, who over time are more prone to develop cognitive problems and symptoms refractory to medication that could reduce benefit and increase their level of disability. Such complications would tend to increase the likelihood that such patients become lost to follow-up. Consistent with this suggestion, the patients lost at follow-up in this study were of significantly older age at disease onset. Given that many patients undergoing DBS are in their 60s or older, attempting to translate the current findings from a cohort of younger patients to older patients undergoing DBS may be problematic.

Other concerns in this article include the lack of neuropsychological data, the fact that 7 out of 18 patients followed long-term had a prior pallidotomy, and no clear indication of whether these 41 patients represented a continuous patient series or were selected on the basis of some other criteria. This is a busy surgical group and operating on 41 patients over a 4- to 5-year span seems low, leading to questions of how the study cohort was established and whether this could also contribute to a biased data set. If these patients do not represent a continuous data set, it would be important to know how these particular patients were selected and why others were not. Knowing the outcomes of patients who were implanted during this time but who were not enrolled could be of equal value to the field.

Another factor that can affect the interpretation of these types of data is the variable duration of the wash-out or wash-in periods (or both) for DBS therapeutic effects [4]. An adequate wash-out period has been demonstrated to require an average of at least 2 hours [5]; the wash-out/wash-in period in this study was 60 minutes, which was adopted to represent 'the best compromise to allow reliable assessments and minimize patient discomfort' [1]. Allowing only 1 hour for DBS effects to reach a maximum may be insufficient and lead to an error that underestimates the benefit of stimulation. However, if the time off medication is not adequate, the error would overestimate the effect of stimulation. There is no way to know, based on the description in the Methods section, whether the short period between conditions could have biased the data set one way or the other. The lack of lead location data in this study, though not necessarily invalidating the message, makes it difficult to determine whether those who maintained long-term benefit had similarly placed leads. I have yet to see a Methods section that does not say that all leads were perfectly placed. Stating that 'postoperative magnetic resonance imaging was performed in all patients to confirm the electrode position' [1] implies that one knows the location of the lead relative to the target. Given that the STN is very difficult to localize using magnetic resonance imaging and that lead artifact can be substantial, such a statement implies that the authors could determine this, which seems unlikely given that it is still very difficult to do today. One of the biggest early and current problems with STN DBS is how to ascertain the precise location of the lead relative to the target with postoperative imaging.

Given the nature of these types of studies and available technology, some weaknesses cannot be helped but nonetheless limit our ability to apply these data to the majority of patients currently considering or undergoing DBS for advanced PD. The bottom line is that we can state that some young-onset patients who received DBS in their 50s may see continued benefit in motor signs and quality of life at 10 years. What we cannot conclude from these data is whether these findings will translate to the majority of patients undergoing DBS who are significantly older, whose disease manifested later in life, and in whom surgical therapy is generally associated with less benefit than those who undergo surgery at a younger age.

On the other hand, these data were collected from patients implanted early in the course of our experience with DBS by using continuous stimulation paradigms. For this group of patients, I would argue that we may do better in the future as we develop new technology, enhance our understanding of optimal target locations

[6,7], and apply new stimulation paradigms based on a better understanding of DBS mechanisms [8-10]. These data also drive home the fact that we must find solutions to treat the axial motor signs of PD which are greatly debilitating to patients, leading to falls, fractures, and marked compromise in quality of life. We need to refocus our efforts by exploring new targets [11,12], stimulation parameters and paradigms (for example, [13,14]), and technology that takes into account the anatomic variations of different targets and begin to explore the possibility of targeting locomotor centers and fiber tracts for gait and balance problems associated with PD [10,12]. Further advances in our understanding of the pathophysiological basis underlying the development of these motor and non-motor signs as well as a firm understanding of the mechanisms underlying DBS as a therapeutic approach will be critical in this regard. The relevance of this approach extends beyond that of PD therapeutics and was recently explored for the treatment of memory disorders and Alzheimer's disease [15]. Whether we can modulate brain circuits adequately for Alzheimer's disease or other, as-yet-unexplored circuit disorders remains to be determined. However, I would add a note of caution: although DBS allows us to 'explore' new targets for new disorders, we do not do so with impunity. We need to explore these targets and disorders on the basis of a well-developed rationale that balances the risks and benefits associated with these approaches.

Conclusions

This study provided evidence that STN DBS can provide significant benefit to parkinsonian motor signs for as long as 10 years while reducing medication requirements below that at the time of surgery. While appendicular signs retained benefit during this time, axial symptoms break through or progress or both, becoming a major source of disability. Given the age of the patient population in this study, young onset, and loss of over half of the patients to follow-up, it remains unclear whether the current data can be used to predict long-term outcome for the majority of patients undergoing this surgery. Nonetheless, the long-term benefit of STN DBS for this subset of patients is highly encouraging, and although many questions remain, the efficacy of this tool will only get better as we continue to improve our understanding of the diseases we treat, the mechanisms underlying DBS's therapeutic effect and advance the technologies that take advantage of that knowledge.

Abbreviations

DBS, deep brain stimulation; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

Competing interests

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