Parkinson’s disease and early subthalamotomy

TO THE EDITOR: We thoroughly read the article by Jourdain et al.9 (Jourdain VA, Schechtmann G, Di Paolo T: Subthalamotomy in the treatment of Parkinson’s disease: clinical aspects and mechanisms of action. J Neurosurg 120:140–151, January 2014), who reviewed subthalamotomy as a surgical treatment for Parkinson’s disease (PD). The authors suggested a positive symptomatic effect of surgery on the cardinal motor features of PD, although the valid data are still somewhat limited and there is no Class I evidence yet. Parkinson’s disease is a progressive, neurodegenerative, and disabling motor disorder, and the pathology is a consequence of the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc). The authors describe research results on subthalamotomy and its possible neuroprotective effect. We have chosen to take a different perspective by stressing the putative role of subthalamic nucleus (STN) lesions in the modification of PD evolution. For many years it has been known that the parkinsonian state is associated with features enhanced glutamatergic (excitatory) STN over-activity, which, in turn, could lead to increased dopaminergic cell loss in the SNc, and subthalamotomy could interfere with such putative excitotoxicity. Admittedly, experimental evidence has shown some variable outcomes, but the aforementioned authors failed to demonstrate the neuroprotective effect of 6-hydroxydopamine (6-OHDA) in a rat model9,10,13–15 or in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).5,8,17 Authors of another article reported no cell-sparing effect of the STN lesion in monkeys treated with MPTP after subthalamotomy.8 However, that study cannot be taken into consideration, as its aim was not the identification of the neuroprotective effect of an STN lesion but rather to ascertain the anti-parkinsonian impact of unilateral subthalamotomy.3 Indeed, another prospective study in the MPTP-treated monkey model assessed the impact of STN lesions, and deep brain stimulation of the STN maintained the excitotoxicity hypothesis. The study demonstrated that STN alteration offered neuroprotection to dopaminergic cells.15 More recently, Jourdain et al. observed no changes in tyrosine hydroxylase immunohistochemistry after a unilateral STN lesion.5 Thus, research analysis suggests that the main factor regarding the hypothetical neuroprotective effect of an STN lesion is inversely proportional to the striatal depletion.

We suggest that for subthalamotomy to be neuroprotective, as with any other possible therapy,1,2 it should be applied very early after diagnosis. Recently, Kordower et al. demonstrated that the loss of tyrosine hydroxylase in the dorsal putamen fell to 35%–75% at 1–3 years and 70%–90% at 5 years after diagnosis.7 This indicates that the time around diagnosis is crucial to protect remaining dopaminergic nigrostriatal cells. Indeed, STN over-activity and the associated excessive glutamatergic release are likely to be present very early after nigrostriatal damage has begun.11,16 Accordingly, clinical trials in patients with advanced PD are of no value when considering neuroprotection.

The recent introduction of a novel and noninvasive surgical treatment, transcranial magnetic resonance—guided focused ultrasound (MRgFUS), could provide such an opportunity if the lesion of the basal ganglia target can be used as well, as has been done in the case of thalamic ventral intermediate nucleus ablation.2 Magnetic resonance—guided focused ultrasound generates an intracranial lesion and provides clinical benefit to patients with disabling tremor if lesion placement and volume are accurate. Initial reports suggest that the procedure is safe enough to proceed with more comprehensive clinical trials. The possibility of practicing targeting with real-time clinical assessment and MRI monitoring opens a new window to future surgical treatments for movement disorders.

When considering a lesion of the STN, the fear of inducing a hemichorea-hemiballism is indeed a concern. We have argued before that the parkinsonian state, by virtue of the changes occurring in the basal ganglia, increases the threshold for hemiballism after STN lesioning.3,4 Indeed, the incidence of hemichorea-hemiballism is about 15% in our experience1 and persists in 9% in whom the dyskinesia is considered severe, and it is not yet known if the volume and location of the lesion or the patient phenotype makes some patients particularly prone to this complication. The clear advantage of focused ultrasound therapy is that the lesion can be formed slowly and progressively, allowing adjustment of its size and permitting physiological compensatory mechanisms to take place. In conclusion, there may yet be another revival of the oldest approach for functional neurosurgery of movement disorders with a newer technique. Proving this could impact PD’s progressive evolution.

Jorge Guridi, MD, PhD
Jose A. Obeso, MD, PhD
Clinica Universidad de Navarra, Pamplona, Spain
References


Response

First, we thank Guridi and Obeso for their insightful comments. The purpose of our article was to uncover the clinical aspects, complications, as well as the biochemical and cellular effects of subthalamic lesions. Guridi and Obeso present their perspectives on the possible neuroprotective effect of this lesion-based surgery for PD, which they say are in opposition to those in our review article. But we do not disagree with these authors. Subthalamotomy may indeed be neuroprotective, but several factors must be considered.

Glutamate plays a major role in the motor pathways of the basal ganglia. The STN is the only source of glutamate intrinsic to the basal ganglia. Although there is no direct evidence of a role for glutamatergic excitotoxicity in PD, several lines of evidence do suggest a toxic effect.2,12 The progressive loss of dopaminergic cells in PD causes the STN to disinhibit. In fact, there is much evidence of increased activity in the subthalamic neurons in both PD patients and animal models of PD.3,26 Such an increase in STN activity in PD raises the possibility of a contribution to degeneration.

The connection between the STN and the SNc is well established.5,17 This subthalamogiral glutamate-enriched pathway may promote sustained excitation of dopaminergic cells. In fact, lesioning of the STN causes selective loss of striatal dopamine in otherwise normal monkeys.20 In the presymptomatic phase of PD, STN-increased activity is believed to serve as a compensatory mechanism for the loss of dopamine.4 However, it may exert an opposite effect in the long term. In fact, because of a high expression of glutamate receptors,13 dopaminergic neurons may become highly sensitive to increased glutamatergic stimulation, and oxidative stress10 and its neuronal degeneration may accelerate.

Subthalamotomy is one of the options currently offered to patients with disabling levodopa-induced dyskinesia,1 which comes late in the disease, after several years of treatment.9 As mentioned in our review, neuroprotection cannot be considered in this clinical setting. As pointed out by Guridi and Obeso, as well as other authors,16 neuroprotection in advanced PD is too late. Therefore, the key factor is an early but accurate diagnosis. Spatial covariance analysis of the resting state metabolic network is among one of the best tools for accurate differential diagnosis.34 On the other hand, an early diagnosis is much harder to achieve. Although transcranial MRGBUS may be a novel, noninvasive surgical treatment for PD, the mentality of neurosurgeons should move from a reactive to a proactive state in favor of neuroprotective surgery. In fact, there is a trend toward such a change.16 Still, we agree that neuroprotection could be achievable within a short time frame after a very early diagnosis. A question remains: Would a subthalamotomy very early after diagnosis be enough to slow down the degeneration? Wallace and colleagues demonstrated a neuroprotective effect of subthalamotomy when performed before exposure to the neurotoxin MPTP.22 In that study, the monkeys were ex-