Deep Brain Stimulation in Parkinson's Disease and Essential Tremor: In Search of Lost Time

Nour E. Yaghmour MD PhD[1], Zvi Israel MD[2], Hagai Bergman MD PhD[2,3,4], Renana Eitan MD[4] and David Arkadir MD PhD[1]

Departments of [1]Neurology, [2]Neurosurgery, and [3]Medical Neurobiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[4]Safra Centre for Brain Research, The Hebrew University, Jerusalem, Israel

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The symptomatic benefit from deep brain stimulation (DBS) in patients with either Parkinson's disease (PD) or essential tremor (ET) is well established. Since electrode placement is an invasive procedure, with infrequent but existing complications, DBS is usually offered to patients with motor symptoms that are not optimally controlled with oral medications. From this common ground, evidence-based clinical decisions are split between PD and ET.

In PD, the majority of patients who require symptomatic treatment enjoy at least a few years of good symptomatic control, a "honeymoon" period. This period ends when motor fluctuations gradually appear. Initially, the patient can overcome these fluctuations by adjusting the regimen of medications. For example, reducing the time intervals between doses of levodopa or adding catechol-O-methyltransferase (COMT) inhibitors could overcome episodes of early 'wearing-off', while starting amantadine could reduce levodopa-induced dyskinesia. For a significant fraction of PD patients, especially those with early onset, such adjustments are not enough. These are the patients who would benefit from DBS targeted to either the subthalamic nucleus (STN) or to the internal globus pallidus (GPi).

The clinical time course described above dictates the optimal timing for DBS in PD. Until recently the average time interval between disease onset and DBS was about 14 years [1,2]. Based on the EARLYSTIM study [3] that was published in 2013, this clinical practice is gradually changing. That study shows that relative to optimal medical therapy, DBS plus medical therapy is superior in PD patients with early motor fluctuations (disease duration 7.3 years) in improving patients' quality of life and controlling their motor symptoms. The EARLYSTIM study opened the door to evidence-based referral of PD patients to DBS in earlier stages of their disease, although controversies regarding this issue still exist [4].

For ET, the clinical picture is different. The age of onset is more variable than in PD, and, based on limited data, it seems that the rate of progression is slower [5,6], at least for younger patients (many of them not even diagnosed). In contrast to PD, in ET the rate of success in ameliorating disabling tremor by the use of oral medication is relatively low. Only 50% of the patients with ET who require symptomatic treatment for their tremor experience a long-lasting effect [7]. Moreover, even these responders experience on average only a 50% reduction in the amplitude of their tremor, which is not sufficient to significantly improve their disability. Patients with refractory disabling ET are referred to DBS of the ventral intermediate nucleus of the thalamus (VIM).

When it comes to ET, DBS is not without problems. The majority of ET patients undergoing this procedure have an immediate clinical benefit, but action tremor reappears after a few months in about one-third of patients [8]. Also, the reported frequency of adverse events in VIM-DBS, mainly dysarthria and ataxia in bilateral procedure, is relatively high [9]. While the optimal time to refer a PD patient is studied, discussed and debated in the medical literature [3,4], similar studies do not exist for ET. The best time to refer a patient with ET to DBS, given disease progression, the limited efficacy of oral therapy and the benefit-to-risk ratio of VIM-DBS, is a matter of personal experience of experts in this field.

In this issue of *IMAJ*, Kestenbaum et al. [10] shed light on this unresolved issue. They report the preoperative clinical characteristics of PD and ET patients who underwent DBS surgery between the years 2009 and 2014. They also compared these patients to a group of randomly selected patients treated conservatively. In their cohort, patients with ET were operated on 25 years after tremor started. For comparison, patients with PD were operated on much earlier – around 11 years after diagnosis. This long period between the appearance of symptoms and DBS surgery in ET might reflect the slow progression of this disease. Alternatively, it could reflect the clinical experience that the benefit-to-risk ratio for DBS in ET is lower than in PD. The authors' finding that impairments in activities of daily living are present in 73% of non-operated ET patients indicates that this second explanation might play a role in delaying surgery.

The limited success of DBS in ET encourages efforts to improve the long-term outcome of this treatment. These efforts included attempts to stimulate other brain areas such as the STN or caudal zona-

incerta [11] or using different parameters for stimulation [12]. While the jury is still out on this matter, the use of an alternative surgical technique, e.g., unilateral focused ultrasound thalamotomy [13] accelerates. If this new technique proves to have a better benefit-to-risk ratio, the 'lost time' between symptom onset and surgical intervention may be reduced.

Correspondence
Dr. D. Arkadir
Dept. of Neurology, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel
Phone: (972-2) 677-7111
email: arkadir@hadassah.org.il

References

1. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998; 339 (16): 1105-11.
2. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006; 355 (9) 896-908.
3. Schuepbach WMM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Me*d 2013; 368 (7): 610-22.
4. Mestre TA, Espay AJ, Marras C, Eckman MH, Pollak P, Lang AE. Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease – the EARLYSTIM trial: early is not always better. *Mov Disord Off J Mov Disord Soc* 2014; 29 (14): 1751-6.
5. Putzke JD, Whaley NR, Baba Y, Wszolek ZK, Uitti RJ. Essential tremor: predictors of disease progression in a clinical cohort. *J Neurol Neurosurg Psychiatry* 2006; 77 (11): 1235-7.
6. Louis ED, Faust PL, Vonsattel J-PG, et al. Older onset essential tremor: more rapid progression and more degenerative pathology. *Mov Disord* 2009; 24 (11): 1606-12.
7. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. *Lancet Neurol* 2011; 10 (2): 148-61.
8. Hariz MI, Shamsgovara P, Johansson F, Hariz G, Fodstad H. Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor. *Stereotact Funct Neurosurg* 1999; 72 (2-4): 208-18.
9. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. *J Neurosurg* 2006; 104 (4): 506-12.
10. Kestenbaum M, Robakis D, Ford B, Alcalay RN, Louis ED. Clinical characteristics of Parkinson's disease and essential tremor patients undergoing deep brain stimulation surgery at Columbia University Medical Center 2009–2014. *IMAJ* 2016; 18: 386-90.
11. Blomstedt P, Sandvik U, Linder J, Fredricks A, Forsgren L, Hariz MI. Deep brain stimulation of the subthalamic nucleus versus the zona incerta in the treatment of essential tremor. *Acta Neurochir* (Wien) 2011; 153 (12): 2329-35.
12. Reich MM, Steigerwald F, Sawalhe AD, et al. Short pulse width widens the therapeutic window of subthalamic neurostimulation. *Ann Clin Transl Neurol* 2015; 2 (4): 427-32.
13. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* 2013; 369 (7): 640-8.