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WHEN TO CONSIDER DEEP BRAIN STIMULATION IN THE TREATMENT OF PARKINSON'S DISEASE

Abstract: Parkinson's disease (PD) is neuropsychiatric disorder caused by selective degeneration of the dopaminergic neurons of substantia nigra pars compacta. Dopaminergic therapies such as levodopa have provided significant benefit and revolutionized the treatment of this disorder. However, the long-term use of levodopa produce complications such us highly disabling fluctuations and dyskinesias which represent one of the major challenge to the existing drug therapy of PD. Deep brain neurostimulation (DBS) is an established treatment for motor symptoms in advanced PD, although concerns exist regarding the safety of this therapy in terms of cognitive and psychiatric adverse effects. This brief overview will address complex interaction of motor and non-motor symptoms of PD and their significance when determining candidate for treatment with DBS.

Key words: *Parkinson's disease, deep brain stimulation, indications*

INTRODUCTION

Parkinson disease (PD) is characterized clinically by motor features (rest tremor, rigidity, bradykinesia) and pathologically by degeneration of nigrostriatal dopamine neurons. In addition other motor signs associated with nondopaminergic transmission (postural instability and impairment of gait, speech, and posture), and non-motor symptoms appear with disease progression. PD is still an incurable progressive disease, but dopaminergic therapies such as levodopa have provided benefit for millions of patients and revolutionized the treatment of this disorder. However patients continue to experience disability despite the best of modern treatment [1, 2]. Over the past two decades, surgery with deep brain stimulation (DBS) has become an accepted treatment for movement disorders, and probably represents the major therapeutic breakthrough of the past 25 years for the management of PD. In patients with PD who exhibit either motor complications arising from long-term

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levodopa therapy, or severe tremor, DBS is now considered to be a routine and evidence based therapeutic option [3–5].

Regarding clinical phenotype PD is a complex and progressive disorder, with varying signs and symptoms. An age of onset, specific clinical features and distribution of motor phenomenology, rate of disease progression, specific constellation of motor and non-motor signs and symptoms can differ significantly among patient's and are important to take into consideration when determining different therapeutic options including candidate for treatment with DBS [6]. In recent years as the evidence base continues to evolve, many important issues have surfaced, including: when to operate, who should and shouldn't be operated on, and finally, why to operate. This brief overview will address each these critical issues to help clinicians in targeting potential candidate for this type of treatment. Details of other important issues such as: mechanism of DBS action, as well as of preoperative protocol and procedures, target selection (subthalamic nucleus (STN) vs globus pallidus internus (GPi)), technical and hardware issues, and postoperative programming are beyond the scope of this paper, and readers are advised to refer to a recent important articles [3,4,7,8].

PATIENT SELECTION

Certainty of diagnosis

Surgery treatment is only effective and appropriate for patients with idiopathic PD, and generally not helpful for patients with atypical parkinsonism [9]. Thus, verification of the diagnosis of PD is the first step in assessing a candidates for treatment with DBS (Table 1). Multiple system atrophy (MSA) is the commonest pathologically confirmed misdiagnosis in patients who have inadvertently undergone DBS. These patients experience little if any benefit from the procedure, and in some, motor disability rapidly increases in the months after surgery [10–12]. Sudden death soon after surgery is also a major risk [12,13]. In the light of recently described MSA cases with slow progression and prolonged survival, specific clinical „red flags" should be taken in consideration in addition to well established diagnostic criteria [14].

Identification of specific motor and non-motor symptoms, therapy complications and their disability

Motor symptoms

Motor control is the main DBS treatment goal for patients with PD. It is now clearly recognized that DBS of the STN or GPi improves the cardinal motor features of PD, especially tremor and bradykinesia, and in some instances disturbance of gait [9]. For example in a meta-analysis of 38 short-term studies from 34 neurosurgical centres in 13 countries, STN DBS improved rigidity and bradykinesia by 63% and 52%, respectively, after 12 months [15]. With the addition of dompamine replacement therapy (DRT), these improvements increased to 73% and 69% respectively. In addition, a reduction of motor fluctuations as well as dyskinesias are com-

monly seen following surgery. For example clinical trials and meta-analyses have assessed the beneficial effects of STN DBS in reducing motor fluctuations, with stable benefits that last for several years after surgery. Similarly, dyskinesia reduction has been consistently reported after STN implantation, owing to the reduction of postoperative dopamine replacement therapy (DRT) by an average 60% [16,17].

Parkinsonian tremor is thought to result from oscillating networks within basal ganglia circuits, and various nuclei within and outside the basal ganglia are potential targets for managing tremor. According to a traditional symptom based approach, lesions or DBS of the thalamic Vim relieve tremor [4,18].

Speech disturbance, swallowing difficulties, severe postural instability and freezing of gait (FOG) usually occur in the late stages of PD, on average 10–15 years after onset, that might be particularly resistant to both DRT and DBS [1,2,4]. It especially came true for severe disturbance of gait unimproved by medication or that occurs predominantly when patients is otherwise in good state (during „ON" period). On the other hand when these symptoms are troublesome during „off" periods alone, some benefit may still be obtained from DBS [4,9].

The vast majority of non-motor symptoms especially cognitive dysfunctions and dysautonomia do not appear to benefit from DBS. Recognizing the motor and non-motor symptoms that contribute to patient's disability and the extent to which the patient's most troubling symptoms may respond to DBS will help to identify those patients who will experience the greatest benefit for this specific type of treatment.

Cognitive and psychotic symptoms

Cognitive problems, including dementia, as well as hallucinations are common in patients with PD, with the prevalence increasing with advanced age and disease progression. These symptoms may be a result of the disease process but also exacerbated by DRT used to control the motor symptoms of PD [1,2].

It is well established criteria do not offer DBS to patients with *bona fide* dementia [9]. The presence of dementia is a marker for less robust motor response to DBS, produce practical obstacles to achieving optimal outcomes, make difficulty cooperating during preoperative and surgical procedures [7]. Less is known about the cognitive and mood sequela of DBS surgery. The most common cognitive issue that has emerged has been reduction in verbal fluency (patients may complain they cannot get words out of their mouth) [4,9]. This problem has been demonstrated in multiple studies, and patients with pre-existing severe cognitive disabilities may experience a worsening of their cognitive status following DBS surgery, leading to more disability. Besides a postoperative decline on a phonological verbal fluency task, long-term cognitive follow-up revealed a slight but significant decline in tasks of episodic memory, executive function, and abstract reasoning [16].

It is generally accepted that Mini Mental Status Exam (MMSE) score £ 24 is an indicator for poor candidacy for surgery. Recently, Montreal Cognitive Assesment (MoCA) and measures of general cognitive functioning, such as Mattis Dementia Ratting Scale (MDRS) has been suggested as a more appropriate cognitive screening tests [9].

Similarly, patients with active hallucinations or delusions may be at increased risk for psychiatric and cognitive complications after DBS surgery [4]. Thus, patients with significant, unresolved psychotic symptoms should not undergo DBS surgery. However, in many instances, reduction or change of anti-parkinsonian medication or addition of an atypical antipsychotic agent can improve these symptoms, with the patient then able to proceed DBS surgery. Certainly, if a patient's psychotic symptoms are mild and clearly medication-induced, then treatment with DBS may be beneficial, since postoperative reduction in medication, and its associated adverse effects, its often possible [7].

Mood disorder and psychiatric symptoms

More than half patients with PD have developed depression, anxiety, and/or apathy [19]. The literature is conflicted on the effect of DBS on mood. Some studies suggest improvement of mood after surgery, however, a growing body of literature suggests that, in some individuals, depression and anxiety can worsen or appear after DBS surgery. Although, there is no clear evidence that presence of pre-existing mood disorder increases risk of postoperative disturbance in mood, it is recommended that before proceeding with surgery, mood disorder have to be identified and effectively treated [4]. Furthermore, DBS surgery should not be offer to the patients with active major depression and to the patients not adequately respond to pharmacological treatment [7].

The association between DBS surgery and suicide behaviours (defined as either suicide attempts or suicide completion) remains controversial. Case reports and observational studies, often with long-term follow-up, have suggested that DBS leads to suicide attempts or completed suicide in a subset of PD patients [20–22]. In a retrospective survey of a large number of PD patients undergoing DBS surgery, the 4-year attempted or completed suicide frequency was 1.4%, which the authors concluded was elevated compared with the general population based on epidemiological data [23]. However, results from recent the randomized, controlled phase of a DBS surgery study in 468 PD patients do not support a direct association between DBS surgery and an increased risk for suicide ideation and behaviours [24].

Up to 13·6% of patients with Parkinson's disease develop impulse control disorders (ICDs) [24], and punding and dopamine dysregulation syndrome (DDS) appear in 15% and 3% respectively [24,25]. DRT might play an important pathogenic part in those repetitive behavior by over stimulating mesolimbic-dopaminergic circuits that are involved in motivation and response to reward [4, 26]. At present level of knowledge the effect of DBS on pre-existing ICDs is still not clear. In majority studies, ICDs improved or disappeared after DBS, but a few studies have reported onset of ICDs (pathological gambling, hypersexuality, and compulsive eating) in patients with Parkinson's disease after DBS despite a postsurgical reduction of DRT [for review see ref 4]. Neuropsychological tests done in PD patients with DBS showed impairment in decision making with increase impulsive choice [28] and loss chasing behavior [29] in some studies, whilst others found an improvement in learning behaviour. [30]. Recent results imply that dopamine agonist therapy but

not deep brain stimulation lead to „reflection impulsivity" in PD, and authors suggest that STN-DBS in combination with L-dopa therapy may be considered as a potential treatment for PD patients with problematic ICDs [31].

Patients with dopamine dysregulation syndrome (DDS) develop an addictive pattern of DRT use. In a series of 21 patients with Parkinson's disease who underwent bilateral STN DBS, symptoms improved or resolved in 29% of the patients with preoperative DDS, however in minority symptoms of DDS appeared only after surgery [32].

Punding is a stereotyped behaviour that characterised by intense fascination with complex, excessive, non-goal-oriented, repetitive activities, and is linked to dyskinesia severity, DDS, and occurrence of other ICDs [26]. Punding is triggered by DRT and can worsen or even arise after DBS surgery, despite DRT reduction [32].

Much of the available literature on the relationship between ICD's and DBS lacks methodological rigor. By prospectively monitoring patients prior to and after invasive procedures with standardized assessments, we will be better able to understand the potential benefits and risks of DBS as it pertains to ICD's, punding and DDS [7].

STATUS OF PHARMACOLOGICAL TREATMENT

Symptoms and signs resistant to appropriate DRT will likely be resistant to DBS with one notable exception of medication-resistant tremor [7]. In addition, DBS is not thought to alter disease progression. Because of this to deem medication treatment sufficiently ineffective before proceeding DBS, one needs to ensure the patient's medication regimen has been optimized for particular symptoms [9]. The basic strategies to optimize pharmacological treatment are listed in Table 2.

It is imported to highlight that in some patients, medications are effective for troublesome motor symptoms but are poorly tolerated, for example because of hallucinations or severe ICDs. Proceeding to surgery earlier, without exhausting all medication options, may be rational in this particular situation [7,9].

The degree to which a patient is responsive to DRT, particularly l-dopa, generally predict how responsive motor symptoms will be to DBS. In addition to careful history of l-dopa efficacy, objective confirmation of l-dopa responsiveness is very helpful [9]. The most widely used scale to assess motor signs of PD is motor subscale of Unified Parkinson disease rating scale (UPDRS). The minimal degree of improvement required between „off" and „on" state is not well established, although majority clinicians desire at least 30% improvement in UPDRS motor score [9]. One exception may be tremor-dominant form of PD, as is well known that tremor is not „pure" dopaminergic sign [1,2]. Okun and Foote [7] highlighted that the major unanswered question for DBS therapy has been when to say enough is enough, and to proceed to DBS therapy. Most practitioners agree that when medication intervals become very close in time (within 2–3 h), and on–off fluctuations, dyskinesia or tremor emerge and are difficult to control, then it is time to at least consider the use of DBS therapy.

UPPER AGE LIMIT AND DISEASE DURATION

The value of age as an independent outcome predictor for DBS has been debated, although there are insufficient data to establish a clear age cut-off. The major concerns with age have been the associated comorbidities, cognitive decline, higher incidence of dopamine resistant symptoms, and higher overall risk of surgical complications [9]. Nevertheless, patient should not be exclude from surgery based on age alone. If older patients experience severe motor fluctuations, dyskinesias, a good respond to l-dopa, no signs of dementia or major psychiatric disturbance, and are in good general health, surgery should be offered [9].

Disease duration has not been a primary factor in dictating the selection of patients with PD for DBS therapy. Historically, patients with PD who have DBS have had disease durations of 10 to 15 years; however, preliminary evidence suggest that DBS may have a greater beneficial effect on quality of life for patients with less advanced disease [4,7,9]. A large randomized controlled trial (EARLYSTIM) involving multiple centres in Germany and France assessed the efficacy of DBS of the subthalamic nucleus combined with best available medical treatment in 251 patients who were younger and had less advanced disease than those currently selected for DBS [33]. The mean age of enrolled patients was 52 years, with mean disease duration of 7.5 years and mean duration of motor complications of 1.7 years. The study reached its primary end point: quality of life as assessed by the 39-Item PD Questionnaire was considerably improved after 24 months in patients receiving DBS compared with the group receiving medical treatment alone. Several secondary outcomes also favored DBS. Whether these results will change current clinical practice and substantially increase the number of patients with PD who receive DBS is, however, uncertain, at least in the short term [34].

CONCLUSION

In conclusion, DBS for PD is currently offered to patients with medication refractory on–off fluctuations, dyskinesia or tremor. In use of DBS, appropriate patients selection is a major determinant of successful postoperative outcome. Of note, nowadays the role of DBS is viewed as means of maintaining motor functions before significant disability ensues, rather then being a last-resort intervention for end-stage disease patients with no other treatment options.

Table 1. Characteristic features of idiopathic Parkinson disease [1, 9]

• Presence of at least two of the three cardinal features of parkinsonism • (rest tremor, rigidity, bradykineasia)
• Asymmetrical onset of signs and symptoms
• Excellent and long-lasting (> 5 years) response to l-dopa
• Absence of features suggesting alternative diagnosis (< 3 years from diagnosis)
– prominent postural instability
– freezing phenomena
– hallucinations unrelated to medications
– dementia, especially if preceding motor symptoms
– vertical supranuclear gaze palsy
– severe symptomatic dysautonomia
– prominent vascular changes on brain MRI
– cortical focal signs (apraxia)
– Upper motor neuron signs

Table 2. The basic strategies to optimize pharmacological treatment in PD

29. Administer immediate release l-dopa at the appropriate dose and frequency. This is five or more times a day in fluctuated patients
30. Add dopamine agonist at appropriate dose to l-dopa if tolerated. If one agonist is ineffective consider trial of another
31. Use catechol-O-methyltransferase (COMT) inhibitor to maximize the duration of l-dopa or to avoid dyskinesias
32. Use monoamine oxidase B (MAO-B) inhibitor to increase „on" time
33. Use amantadine up to two times a day to treat troublesome dyskinesia
34. Use anti-cholinergic medication if the patient has severe tremor or dystonic oro-facial dyskinesia
35. Consider the use of rescue dose of apomorphine or l-dopa for unpredictable „off" periods

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