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Benefits of subthalamic stimulation for elderly parkinsonian patients aged 70 years or older

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ABSTRACT

Objectives: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an accepted treatment for advanced Parkinson disease (PD). However, there is general reluctance in considering this therapy for PD patients over age 70 years with limited supporting evidence. Present study investigates age impacts in STN-DBS outcomes, focusing particularly on the elderly patients.
Patients and methods: Seventy-two consecutive patients were divided into younger and elderly (n = 16, cutoff age = 70 years) groups. Both groups were comparable in preoperative clinical severity, except the elderly exhibited a levodopa (LD) response ($P < 0.05$) inferior to that of the younger. Improvements in drug-off/DBS-on Unified PD Rating Scale (UPDRS) scores and reduction in daily LD-equivalent dose (LED) after 6 months were evaluated relative to the presurgical drug-off baseline. Preoperative factors predictive of favorable surgical outcomes were analyzed using a multivariate linear regression model.
Results: After DBS therapy, elderly patients exhibited clinical improvements particularly in the tremor (56%) and LD-induced dyskinesia (78%). Improvement of axial dysfunction (24%) and reduction of daily LED (24%) showed no intergroup difference. Adverse events, particularly dysarthria, occurred frequently in elderly group. The overall improvements in UPDRS scores were suboptimal in elderly group, correlating with their preoperative inferior LD responses. Elderly patients who presented predominantly with akinesia before surgery achieved superior surgical outcomes (adjusted $R^2 = 0.657$, $P < 0.001$).
Conclusion: STN-DBS therapy is beneficial to some elderly PD patients aged 70 years or older. Tremor, axial dysfunctions and drug-induced dyskinesia are the main indications for the elderly; however, their clinical benefits are inferior to those of younger patients.

1. Introduction

Parkinson disease (PD) is a neurodegenerative disorder commonly found in older people [1]. The peak incidence occurs at 60–70 years. The mean age of onset is approximately 60–65 years [2]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is effective in treating patients with advanced PD, typically improving their life quality [3–5]. However, elderly PD patients (age ≧ 70 years) are frequently excluded worldwide from DBS therapy [3,6,7] or related clinical trials [8] on the sole basis of upper-age limits, despite little supporting evidence. Both facts are probably not relevant to PD patients in actual clinical practice.

Some clinical studies have suggested that aging plays a crucial role in the clinical course and therapeutic outcomes of PD. For example, positron emission tomography studies indicate a relatively slow progression of nigrostriatal dysfunctions and more efficient adaptive mechanisms in younger PD patients [9]. Age-related physiological changes in older patients can influence their pharmacokinetics and outcomes of drug therapy [10,11]. The bioavailability of levodopa (LD) is higher in elderly patients than in younger patients. The shape and spatial position of the STN can change substantially with increasing age [12,13].

Few non-randomized Western studies [14–17], but no randomized controlled study, have demonstrated that STN-DBS therapy exerts similar short- to medium-term motor benefits in older and younger PD patients, but does not improve the life quality of elderly patients [14,15,17]. Populations in Asian countries are increasingly aging, and the prevalence and incidence rates of PD in Asian countries are close to those of Western countries [2]. However, the effects of STN-DBS on elderly Asian patients have yet to be elucidated. This paper presents the 6-month outcomes of STN-DBS in elderly PD patients during a 9-year observation period. The potential predictors for favorable surgical outcomes are also described.

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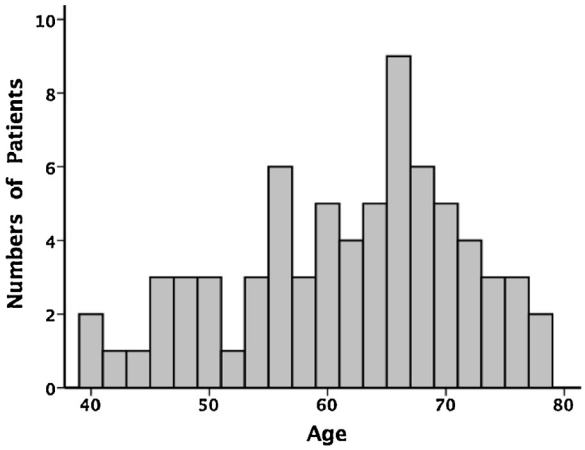

Fig. 1. Age distribution at time of the surgery.

2. Materials and methods

2.1. Patients

Seventy-two consecutive PD patients, aged 40–78 years with disabling motor fluctuations/or dyskinesia despite optimal medical treatment, underwent bilateral STN-DBS therapy within the period May 2004–December 2013 (Fig. 1). Movement disorder specialists screened the surgical candidates according to the CAPSIT-PD criteria [18]. The patients were ineligible for surgery if they had significant cognitive dysfunction as indicated by a Mini-Mental State Examination score (MMSE) less than 20, major depressive disorder or severe concomitant medical comorbidities. Patients were divided into "elderly" (n = 16, aged ≧ 70 years) and "younger" (n = 56, aged <70 years) groups. All patients provided written informed consent approved by an institution ethics committee prior to surgery. This study complied with institutional guidelines and the regulations of the Declaration of Helsinki.

The younger and elderly patients were comparable in preoperative phenotypes and clinical severity, except that the elderly group exhibited lower (34% versus 46%, $P = 0.008$) improvement after LD (1.5x therapeutic dose) acute challenge (Table 1). Significant age-related differences ($P < 0.05$) existed in preoperative LD (normal therapeutic dose) responses (Table 2), as indicated by the lower improvement percentage for the elderly patients in the Unified Parkinson Disease Rating Scale (UPDRS) total score (18% versus 30%, $P = 0.015$), part II subscore (activities of daily living, ADL; 16% versus 35%, $P = 0.011$) and part III (motor, 23% versus 34%, $P = 0.042$) subscores; the difference was particularly evident in the tremor domain (26% versus 52%, $P = 0.013$). However, LD-induced complications (part IV subscore), including dyskinesia, were not significantly different between the two groups.

2.2. Surgical technique and programming

All patients underwent a two-stage operation that employed a standardized stereotactic procedure as described in a previous study [19]. Briefly, STN electrodes (model 3389, Medtronic, Minneapolis, MN, USA) were implanted bilaterally during the first session while the patient was awake following an overnight withdrawal of dopaminergic drugs. The STN was targeted using T2-weighted magnetic resonance imaging and intraoperative microelectrode electrophysiological guidance. After 5 days, an implantable pulse generator (IPG, Kinetra) was placed under general anesthesia. Programming was initiated 2–3 weeks after IPG implantation when the lesion effects had subsided. After optimizing the settings, the stimulator was turned on continuously. The programming parameters indicated no significant intergroup differences.

2.3. Clinical assessments

The patients were initially assessed in the DBS-on state after an overnight medication withdrawal of at least 12 h; and then repeatedly assessed after the DBS-off state began for at least 30 min. Afterwards, we also assessed the patients in medication on/stimulation off state and in medication on/stimulation on state. The same evaluator performed the pre- and post-operative assessments.

The primary endpoint was the changes in the UPDRS scores after 6 months in the drug-off/DBS-on condition relative to the preoperative drug-off baseline. Motor outcome measures focused on speech (item 18), tremor (items 20–21), rigidity (item 22), akinesia (items 23–26) and axial (items 27–30) dysfunctions. Dyskinesia complications (items 32–35) following therapy were also evaluated. The secondary endpoint was the changes in the daily LD-equivalent dose (LED).

2.4. Statistical methods

All data were expressed as mean and standard deviation (SD). A Wilcoxon signed-rank test was used for pre- and post-operative comparisons within groups. The intergroup differences in the UPDRS scores or daily LED were compared using a Mann-Whitney *U* test. A simple linear regression analysis was initially performed to identify the potential prognostic factors for surgical outcomes related to preoperative parkinsonian features including sex, onset or duration of illness, cognition, clinical phenotypes in the drug-off state, and LD response. The dependent variable was always the 6-month reductions in UPDRS motor scores in the drug-off/DBS-on state relative to the preoperative drug-off baseline. Subsequently, independent variables significantly related to the postoperative outcomes were included in a stepwise multivariate linear regression analysis. A *P*-value of less than 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed using PASW Statistics 18 software (SPSS, Inc., Chicago, Illinois, USA).

3. Results

3.1. Surgical outcomes

The present series achieved significant clinical improvements for all UPDRS items at 6 months after DBS surgery (Table 2). The elderly patients did experience surgical benefits particularly in the tremor domain with 56% improvement ($P < 0.05$), nearly twice the improvement rate of medication (26%) before surgery, and a 59% reduction in LD-induced complications ($P < 0.05$). The improved rate (approximately 25%) in axial problems after DBS therapy was similar for both groups without statistically significant differences. However, the improvements in rigidity (3%) and akinesia (8%) as well as ADL (8%) dysfunctions were suboptimal in the elderly patients through DBS therapy. Notably, except in the tremor domain, the improved percentages in the UPDRS total score and subscores postsurgery approximated the range of 80–100% compared with preoperative improvement after medication among the younger patients. By contrast, the improved percentages in the UPDRS total score and subscores achieved after DBS therapy among the elderly patients were much lower (50–80%) compared with those in the preoperative LD response (Table 2).

In the elderly group, the mean daily LED decreased from 623 ± 382 mg presurgery to 474 ± 263 mg (24% reduction, $P = 0.029$) at 6 months postsurgery. In the younger group, the mean daily LED