Short communication

# How many parkinsonian patients are suitable candidates for deep brain stimulation of subthalamic nucleus? Results of a questionnaire

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## Abstract

We used a CAPSIT-based questionnaire to estimate the percentage of parkinsonian patients suitable for subthalamic nucleus (STN) deep brain stimulation (DBS) in a movement disorders clinic. We found that out of 641 consecutive PD patients only 1.6% fulfilled strict STN-DBS criteria. When we applied more flexible criteria, the percentage of eligibility increased to 4.5%. Most patients (60%) were ineligible because they did not satisfy multiple questionnaire items. Items related to disease severity were responsible for the largest number of exclusions. This knowledge will help make decisions on resource allocation in centres wishing to start DBS surgery.
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## 1. Introduction

Bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) is a long-term effective treatment for improving levodopa-responsive symptoms in patients with advanced Parkinson's disease (PD) [1].

Selection criteria for STN DBS have been formulated over the years taking into account the experience of previous surgical treatments [2] and the outcome of the patients who have undergone surgery since 1993 [3]. Most centres with a surgical program refer to the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) [4] for patient selection. More recently, an extensive review of the literature together with expert opinion about criteria for inclusion of DBS in PD has been published [5].

However, few data are available on the percentage of the overall PD population that may be eligible for STN-DBS surgery and on the reasons for exclusion. This is important particularly for new centres wishing to set up a new DBS program. For this purpose we used a specific questionnaire

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based on the CAPSIT criteria protocol to define features that in a clinical setting might be responsible for DBS exclusion.

## 2. Patients and methods

In 2002–2003 we conducted this study in eight Italian Movement Disorders Centres (Ancona, Grosseto, Messina, Milano, Napoli, Roma, Trieste, Pisa-Viareggio), where one or two neurologists expert in movement disorders submitted a questionnaire to a maximum of 100 consecutive patients presenting with a clinical diagnosis of PD. The questionnaire and the design of the study were previously defined during a meeting among the neurologists responsible for the Italian DBS centres. There was general agreement in using the CAPSIT-PD protocol recommendation for the patients' inclusion criteria for STN DBS. Eight movement disorders centres decided to be actively involved in the study. Six were academic institutions, whereas two were movement disorders centres in public hospitals. A period of time of 1 month was considered adequate for collecting the data. Written informed consent was obtained and the study was approved by the local ethics committees.

### 2.1. Questionnaire

The questionnaire consisted of 18 items largely based on the CAPSIT-PD protocol, including patient's clinical features related to PD and to general medical conditions that might be potential contraindications to STN DBS. In each centre the neurologist completed the questionnaire following a face-to-face interview with the subject and evaluation of clinical records (i.e. for the scales required by the questionnaire). If a positive answer was obtained for all the items, the patient was considered eligible for STN DBS.

Sensitivity and specificity of the questionnaire was previously assessed on two samples of 20 PD patients recruited from one of the centres (Centro Parkinson, Milano). The first sample consisted of PD patients who screened positively to CAPSIT-PD and underwent bilateral STN DBS. In other words, the clinical judgment derived from CAPSIT-PD was considered the "gold standard". The second sample consisted of PD patients who screened negatively to CAPSIT-PD and therefore were excluded from STN DBS.

### 2.2. Body of the questionnaire

Each item was inserted in a question which required a "yes" or "no" answer.

(1) PD diagnosis: Patients with probable PD, based on the Gelb and Gilman's criteria [6] were included, whereas patients with other types of parkinsonism were excluded.
(2) Disease duration >5 years: We agreed that 5 year PD duration was the lowest threshold for PD misdiagnosis and for a good medical management of the disease.
(3) Age <70 years: This age limit was decided taking into account the previous negative experience with aged patients [7,8].
(4) Motor complications (motor fluctuations and levodopa-induced dyskinesia) not controlled with optimized medical therapy for at least 1 month.
(5) Hohen–Yahr in off $\geqslant \frac{3}{5}$.
(6) UPDRS-III in off $\geqslant \frac{40}{108}$: This threshold was considered severe enough to justify surgery in patients without marked tremor.
(7) Severe motor disability and need of assistance in many activities of daily living: The entity of the overall disability was determined taking into account the UPDRS-II when off medication and the opinion of the care givers.
(8) Good clinical levodopa response based on medical history: These data were obtained from the previous medical records of the patient (if an acute levodopa challenge was performed in the past) or considering the clinical response of chronic treatment with levodopa reported by the patient.
(9) Absence of major depression and/or major psychosis based on medical history and clinical data.
(10) Absence of current drug-induced psychosis or previous drug-induced psychosis on chronic antipsychotic medication: Since psychosis could possibly interfere with the post-operative management, the agreement was to consider it as exclusion criterion.
(11) Good compliance of the patient and his family.
(12) Strong personal motivation and awareness of disease related problems.
(13) Poor quality of life: The neurologist was asked to investigate items (11)–(13) with specific questions to the patient and care givers.
(14) Absence of clinically evident cognitive impairment: The Mini Mental State Examination (MMSE) [9] was administered to the patient as first screening and a value of MMSE $\leqslant 23$ was chosen as cut-off.
(15) Absence of alcohol or drug abuse.
(16) Absence of systemic diseases or illness that can increase surgical risk and make prognosis worse.
(17) Absence of major risk factors for cerebrovascular disease (cerebral atherosclerosis, uncontrolled hypertension, etc.).
(18) Absence of cardiac pace-maker and anticoagulant treatment which cannot be suspended.

### 2.3. Statistical analysis

For statistical analysis, $\chi^2$ test was used to compare the differences in the percentage of eligibility between groups. A p-value $\leqslant 0.05$ was considered significant.

## 3. Results

### 3.1. Validation of the questionnaire

In the first group of patients ($n = 20$, screened positively to CAPSIT-PD) the true positives were 20 and 0 the false negative. In the second group ($n = 20$, screened negatively to CAPSIT-PD) the true negatives were 18 and 2 the false positives. The two patients who screened positive to the questionnaire, although excluded from STN DBS, had presented with major depression when had undergone CAPSIT-PD 5 months before. They were later treated with antidepressant medications with complete recovery. In conclusion the questionnaire showed a sensitivity of 100% and a specificity of 90% (CI 80–100). The positive predictive value (PPV) was 91% (CI 82–100) and the negative predictive value (NPV) was 100%.

### 3.2. Eligibility for STN DBS

A total of 809 patients with parkinsonism were enrolled in the study (M:F ratio = 1.39:1), but 168 patients (20.7%) were excluded by the first item of the questionnaire. There was no significant difference in the prevalence of PD between the movement disorders centres involved in the study.

Out of the remaining 641 patients with probable PD, only 10 patients (1.6% of the total patients) satisfied all the items and were considered eligible for STN DBS. The percentage of eligibility was higher in women (2.3%) than men (1.1%) where this was not significant. There were no

gender differences in the percentage of positive answers for each item with the exception of absence of severe motor disability (24.6% males vs 33.08% females, $p \leqslant 0.05$), absence of major depression (85.95% males vs 79.8% females, $p \leqslant 0.025$) and poor quality of life (36.7% males vs 46.3 5% females, $p \leqslant 0.025$).

Twenty patients (3.1%) were excluded for one item, mainly for current drug-induced psychosis or previous drug-induced psychosis still treated with antipsychotic medication (45%) and age $> 70$ years (30%) (see Fig. 1). The items correlated with disease severity (absence of severe motor disability, absence of motor complications with stable treatment for at least 1 month, UPDRS $\leqslant 40$ and H&Y $\leqslant 3$) were the most common source of exclusion (see Table 1). In particular, 77.8% of PD patients were excluded because of items 6 and 7. Moreover, 60% of patients were not eligible for multiple items (between 5 and 8).

Considering the subgroup represented by the most disabled PD patients (who answered "yes" to item 7), the percentage of eligibility was 5.5% $(\frac{10}{180})$. We also performed a supplemental analysis using less strict criteria: specifically we did not include item 6 (UPDRS-III in off $\geqslant \frac{40}{108}$) and we raised the age limit to $< 75$ years. With this approach the percentage increased to 3.7% $(\frac{22}{641}$: 13 females, 11 males). Moreover, the percentage of eligible patients increased to 4.5% $(\frac{29}{641}$: 17 females, 12 males) when drug-induced psychosis was not included as criteria together with age and UPDRS $\geqslant 40$.

## 4. Discussion

We administered a specific questionnaire based on CAPSIT to 641 PD patients from eight Italian movement disorders centres and found that the percentage potentially eligible for STN DBS was 1.6%. The items related to disease severity, such as absence of severe motor disability, absence of motor complications with stable treatment for at least 1 month, UPDRS-III $\leqslant 40$ and H&Y $\leqslant 3$, were the

Table 1
Number of positive answers to each item (%)

| Questionnaire items | |
|---|---|
| 1. Parkinson's disease diagnosis | 641 |
| 2. Disease duration $> 5$ years | 449 (70) |
| 3. Age $< 70$ years | 348 (54.3) |
| 4. Uncontrolled motor complications | 198 (30.9) |
| 5. Hohen–Yahr $\geqslant 3$ | 233 (36.3) |
| 6. UPDRS off $\geqslant 40$ | 202 (31.5) |
| 7. Severe motor disability | 180 (28.1) |
| 8. Good clinical levodopa response | 596 (93) |
| 9. Absence of major depression and/or psychosis | 535 (83.5) |
| 10. Absence of current drug-induced psychosis | 377 (58.8) |
| 11. Good compliance of patient and his family | 568 (88.6) |
| 12. Strong personal motivation | 371 (57.9) |
| 13. Poor quality of life | 261 (40.7) |
| 14. Absence of cognitive impairment | 556 (86.7) |
| 15. Absence of alcohol or drug abuse | 613 (95.6) |
| 16. Absence of systemic diseases or illness | 505 (78.8) |
| 17. Absence of major cerebrovascular risk factors | 498 (77.7) |
| 18. Absence of anticoagulant therapy and cardiac pacemaker | 600 (93.6) |

cause of most of the exclusions. Specifically, UPDRS-III $\leqslant 40$ and lack of severe motor disability raised the exclusion to 77.8% patients. Although all the items contributed to the exclusion from STN DBS, alcohol abuse, anticoagulant treatment and absence of good response to levodopa were rare causes of exclusion. Using more flexible criteria the percentage of eligibility increased to 3.7% (including patients with age $< 75$ years and excluding the item UPDRS $\geqslant 40$) and 4.5% (without UPDRS and psychosis criteria and with age $> 75$ years).

Although DBS represents a valid and relatively safe procedure to manage long-term complications in PD [1], there are no data on the percentage of PD patients eligible for STN DBS. Since nine patients (1.4%) were excluded from surgery because of the presence of drug-induced psychosis, it is important to emphasize that the questionnaire was developed 4 years ago, when the involvement of a psychiatrist in the surgical team and management of STN DBS patients was uncommon. Indeed, with the active involvement of a psychiatrist in the pre-operative management, negative psychiatric outcomes can be prevented [10]. Another finding of the study was the same percentage of eligibility for STN DBS in men compared to women. This finding appears in contrast with the results presented in a recent paper by Hariz et al. [11]. They found that surgery for PD is about twice as frequent in males as in females whereas women have a greater improvement in quality of life 1 year after surgery. Our finding supports the interpretation that non-biological and non-clinical factors may account for Hariz's results, since there was no gender difference in eligibility for surgery based on the clinical selection criteria of our questionnaire.

Some possible limitations of the study are linked to the structure of the questionnaire based on the CAPSIT-PD
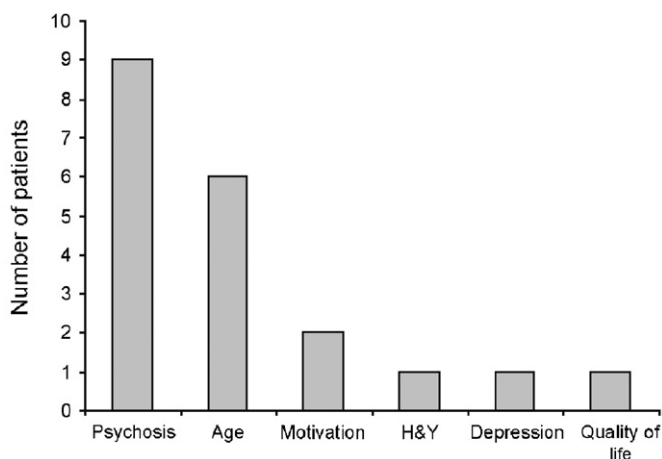


Fig. 1. The histogram shows the items causing the exclusion of 20 patients from STN DBS because of one negative answer to the questionnaire.

protocol. At the time of the study design all the involved Italian DBS surgical centres agreed to the use of strict and rigid criteria for inclusion/exclusion such as the UPDRS-III $\geqslant 40$ (possibly not always reflecting the real disability of the patients, i.e. for tremor-dominant PD a lower UPDRS score could have been accepted) and the lack of proper assessment of medical history data. Our findings are also in keeping with recently published recommendations about inclusion/exclusion criteria for DBS [5]. Indeed, many surgical centres have adopted our UPDRS motor score severity (i.e. $\geqslant 40$) as an indication for surgery. Our questionnaire might have overlooked those young-onset PD patients with a moderate off-score but severe levodopa-induced motor complications. Finally, the MMSE might not be an appropriate instrument with which to detect cognitive impairment in PD patients, but it was the most widely used scale at the time the questionnaire was developed.

It is important to emphasize that our questionnaire has not been designed as a first level instrument for screening a parkinsonian population for surgery, as was recently proposed in a study by Okun et al. [12]. We acknowledge that careful and rigorous examination of patients with adequate neuropsychological assessment and acute levo-dopa challenge represents the gold standard before surgery. The low percentage of eligibility might be understood considering that the questionnaire was administered to a heterogeneous sample of PD patients treated in a move-ment disorders centre, including those in the early phase of the disease excluded by the items related to disease's severity but potentially eligible in the future for STN DBS. On the other hand, our results provide insight about the most frequent cause of exclusion from surgery. Moreover, when we applied more flexible criteria, the percentage of eligibility increased to 4.5% but was not substantially modified since most of the patients (60%) would be excluded because of negative answers to multiple items.

The employment of our simple questionnaire, in spite of its limitations, allowed us to conclude that STN DBS can be reserved for a small percentage of PD patients. Considering previous epidemiological studies performed in Italy [13], which showed a PD prevalence ratio of $\frac{257}{100.000}$ population, it is possible to estimate that the number of patients suitable for STN DBS in Italy is about 2500. We believe our results will facilitate decision making in centres wishing to start a DBS program.

## References

[1] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349: 1925–34.

[2] Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992;7:2–13.

[3] Lang AE, Widner H. Deep brain stimulation for Parkinson's disease: patient selection and evaluation. Mov Disord 2002;17(Suppl 3): S94–S101.

[4] Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkin-son's disease (CAPSIT-PD). Mov Disord 1999;14:572–84.

[5] Lang AE, Houeto JL, Krack P, Kubu C, Lyons KE, Moro E, et al. Deep brain stimulation: preoperative issues. Mov Disord 2006;21(Suppl 14):S171–96.

[6] Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol 1999;56:33–9.

[7] Welter ML, Houeto JL, Tezenas du MS, Mesnage V, Bonnet AM, Pillon B, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002;125:575–83.

[8] Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002;59:932–4.

[9] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[10] Voon V, Saint-Cyr J, Lozano AM, Moro E, Poon YY, Lang AE. Psychiatric symptoms in patients with Parkinson disease presenting for deep brain stimulation surgery. J Neurosurg 2005;103:246–51.

[11] Hariz GM, Lindberg M, Hariz MI, Bergenheim AT. Gender differences in disability and health-related quality of life in patients with Parkinson's disease treated with stereotactic surgery. Acta Neurol Scand 2003;108:28–37.

[12] Okun MS, Fernandez HH, Pedraza O, Misra M, Lyons KE, Pahwa R, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63: 161–3.

[13] Morgante L, Rocca WA, Di Rosa AE, De Domenico P, Grigoletto F, Meneghini F, et al. Prevalence of Parkinson's disease and other types of parkinsonism: a door-to-door survey in three Sicilian municipa-lities. The Sicilian Neuro-Epidemiologic Study (SNES) Group. Neurology 1992;42:1901–7.