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ORIGINAL COMMUNICATION

A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease

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Abstract *Background and objective* Although Deep Brain Stimulation (DBS) has been proven to be an effective treatment for patients with advanced Parkinson's disease (PD), it may be difficult for general neurologists to identify appropriate candidates for this procedure. We developed an electronic decision tool that can assist neurologists in deciding which PD patients should be referred for DBS consideration. *Methods* Using the RAND/UCLA Appropriateness Method, an international expert panel assessed the appropriateness of referral for 972 theoretical patient profiles. Panel results were embedded in an electronic decision support tool which displays the panel statement on referral (appropriate, inappropriate and uncertain) after completion of the patient profile. *Results* Referral was considered appropriate for 33 % of the theoretical profiles. Logistic regression showed excellent internal consistency of the ratings (predictive value 92 %). Symptom severity (OFF-symptoms, dyskinesias, refractory tremor) and PD duration were positively associated with the panel judgment that referral is appropriate. Presence of levodopa-resistant axial symptoms, age ≥ 70 years and presence of cognitive impairment showed the strongest negative impact. *Conclusions* The RAND/UCLA method proved to be useful in determining the appropriate criteria for DBS referral. Validity and applicability of the decision tool (accessible via http://test.stimulus-dbs.org) in clinical practice need to be further determined.

Key words Parkinson's disease · deep brain stimulation · appropriateness method · decision support

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Introduction

Compelling evidence shows that deep brain stimulation (DBS) is an effective treatment for well-selected patients with Parkinson's disease (PD) [10, 17]. In patients insufficiently responding to, or experiencing unacceptable side effects from medical treatment, substantial and long-lasting benefits following DBS have been demonstrated, including improved motor function, reduced dyskinesia, decreased medication usage, and increased quality of life [4, 5, 8, 11, 13, 16, 18, 19]. Patient eligibility for DBS is determined in specialised movement disorders centres using a comprehensive selection process, including a levodopa challenge test, brain imaging and assessment of neuropsychological and psychiatric functions. For general (community) neurologists, it may be difficult to identify patients who could be good candidates for DBS and may be referred to a specialised centre for further evaluation. In a recent US centre review [15], 63 % of patients referred were refused for DBS which underlines the necessity of adequate pre-selection. Conversely, under-referral may also exist, withholding appropriate candidates the opportunity of being assessed by a specialised movement disorder centre.

In order to support appropriate referral, Okun et al. developed a screening tool (printed checklist) for DBS candidates [15]. Although an initial validation of this tool showed favourable results, its application in daily practice may be too complex and time-consuming for community neurologists. We therefore developed a user-friendly electronic decision tool that also allows data storage and patient follow-up.

Methods

In order to combine best evidence from clinical studies and clinical expertise, the RAND/University of California at Los Angeles appropriateness method (RAND/UCLA method) was used [1, 7]. This validated modified Delphi method has been applied to assess the appropriateness of medical and surgical technologies in various fields of medicine [21]. An international panel of 12 experts in movement disorders and DBS rated the appropriateness of referral for DBS for 1728 hypothetical PD patient profiles. These profiles were unique combinations of the values of 9 clinical variables, considered relevant to the decision whether a PD patient should be referred to a DBS centre. Selection of these variables and definition of the study population and clinical conditions was based on a literature review which was discussed with the panel during a plenary meeting prior to the rating process. Panellists used an electronic program to individually assess the appropriateness of referral for all profiles using a 9-point scale (1 = very inappropriate, 9 = very appropriate, 5 = uncertain). Appropriate was defined as the situation in which the potential benefits of referral exceeded the potential negative consequences by a sufficient margin that is worth doing [1]. Considerations other than the patient's clinical conditions (e.g. cost of treatment, waiting lists) had to be disregarded, as well as procedures and decisions that are usually reserved to the DBS centre (e.g. MRI, DBS target). After a plenary panel discussion, final inclusion criteria and definitions were established (Table 1), and a new decision framework was constructed including 7 clinical variables and 972 PD patient profiles (Table 2). Panellists subsequently performed a second rating round. Following mathematical rules that are typically used in RAM studies [7], appropriateness statements for all 972 PD patient profiles were calculated on the basis of the median panel score and the extent of agreement between panellists. For a median score between 7 and 9 without

Table 1 Inclusion criteria and terminology used for the PD patient profiles

Inclusion criteria (absolute criteria for the consideration of DBS)

1. Idiopathic Parkinson's disease:
   a. Presence of bradykinesia plus muscular rigidity and/or rest tremor
   b. Asymmetric onset
   c. Slowly progressive
   d. Lack of prominent dysautonomia
   e. Lack of cerebellar or pyramidal findings
   f. Robust historical response to levodopa
2. Troublesome symptoms despite optimal pharmacological treatment or intolerable side effects related to antiparkinsonian medication;
3. Patient still has clear motor improvement with levodopa;
4. Absence of significant medical conditions which prevent surgery or are associated with a limited life expectancy;
5. Absence of significant medically-resistant mental diseases (e. g. severe depression, severe intellectual impairment).

Troublesome symptoms

Presence of symptoms (on-off fluctuations and/or dyskinesias and or tremor), having a substantial impact on the patient's quality of life.

Optimal pharmacological treatment

Maximum reasonable pharmacological therapy.

Levodopa-unresponsive axial symptoms

Axial symptoms (such as postural instability, freezing, falling, gait hesitation) during ON time, unresponsive to levodopa.

Refractory tremor

Tremor unresponsive to or requiring unacceptably high doses of levodopa.

Intellectual impairment

a. Mild: consistent forgetfulness with partial recollection of events and no other difficulties.
b. Moderate: Moderate memory loss, with disorientation and moderate difficulty handling complex problems.
c. Severe: Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

Table 2 Clinical variables and categories used for assessing the appropriateness of DBS referral (second rating round)

Variable	Categories
Age (years)	a. < 60 b. 60–69 c. ≥ 70
Duration of Parkinson's disease	a. < 5 years b. ≥ 5 years
Severity of symptoms during OFF-state	a. Mild[a] b. Moderate[b] c. Severe[c]
Severity of dyskinesias	a. Mild[a] b. Moderate[b] c. Severe[c]
Levodopa-unresponsive axial symptoms	a. No b. Yes
Refractory tremor	a. No, or mild[a] b. Moderate[b] c. Severe[c]
Intellectual impairment[d]	a. No b. Mild c. Moderate

[a] No or slight impact on quality of life
[b] Moderate impact on quality of life (bothersome to patient)
[c] High impact on quality of life (interferes with many activities)
[d] See Table 1. Severe intellectual impairment was considered as an absolute exclusion criterion

disagreement (≥4 panellists in each of the sections 1–3 and 7–9), referral was considered appropriate. For a median score between 1 and 3 without disagreement, referral was deemed inappropriate. All other outcomes were labelled as uncertain. The results were embedded in an electronic decision support program that displays the panel recommendation for each selected patient profile (Fig. 1).

Statistical analysis

Internal consistency and underlying patterns of the panel statements were analysed using logistic regression with the panel outcome that referral is appropriate as the dependent variable. As explanatory variables all clinical criteria used for the construction of patient profiles (Table 2) were included. All statistical analyses were performed using SPSS for Windows Release 15.0.

Results

Appropriateness ratings

After the second rating round, referral was considered 'Appropriate' in 33 % of the 972 theoretical PD patient profiles. Referral was deemed 'Inappropriate' or 'Uncertain' in 19 % and 48 % of profiles respectively. No single clinical variable resulted exclusively in the attribution to one particular appropriateness category. Logistic regression analysis showed highly significant coefficients for the clinical variables included, all in the expected direction (Fig. 2). Severe tremor, OFF-symptoms and dyskinesias were the most important factors in favour of referral, while the presence of moderate intellectual impairment, age ≥ 70 years and levodopa-unresponsive axial symptoms showed the strongest negative impact. The robustness of the regression model was high (Hosmer-Lemeshow value = 1.0, predictive value 92 % at a cut-off point of 0.5), indicating excellent internal consistency of the ratings. Inclusion of potential interactions (different impact of one variable for different values of other variables) did not significantly improve the predictive value of the model. This means that the panel outcomes were predominantly determined by the sum of positive and negative coefficients.

Electronic decision tool

Based on the panellists' comments and suggestions, a final version of the decision tool was established (Fig. 1). Users are asked to firstly check the absolute criteria for the consideration of DBS (Table 1). If the patient fulfils these criteria, the values for the seven key variables can be entered, after which the program displays the median score and the panel recommendation of appropriateness of referral. The program can be viewed via http://test.stimulus-dbs.org.

Discussion

Adequate screening and selection of PD patients for DBS increase the benefits of this treatment [12, 14], and reduce unnecessary procedures and unrealistic expectations in patients with a less favourable profile. Given the practical limitations in a general neurological setting, the panel faced the challenge to translate highly specialised selection criteria used in DBS centres into concise and easily applicable referral criteria, embedded in a user-friendly decision support tool.

The panel formulated five criteria for which there is considerable evidence that these are absolute prerequisites a patient should meet for considering the possibility of DBS (Table 1). As non-PD parkinsonian patients are expected to have a poor response to DBS [12], the first criterion relates to the diagnosis of idiopathic PD. A concise checklist, based on the PD-UK PDS Brain Bank diagnostic criteria [9], was added to specify this condition (Table 1). The second absolute criterion requires the severity of symptoms, despite optimal pharmacological treatment, to be sufficiently troublesome to justify surgical treatment. A standardised measurement of symptom severity using the Unified Parkinson's Disease Rating Scale (UPDRS) [6] is often too time-consuming for general neurologists. The panel therefore opted for a pragmatic description, based on the neurologist's subjective judgment that motor symptoms (on-off fluctuations and/or dyskinesias and/or tremor) have a substan-

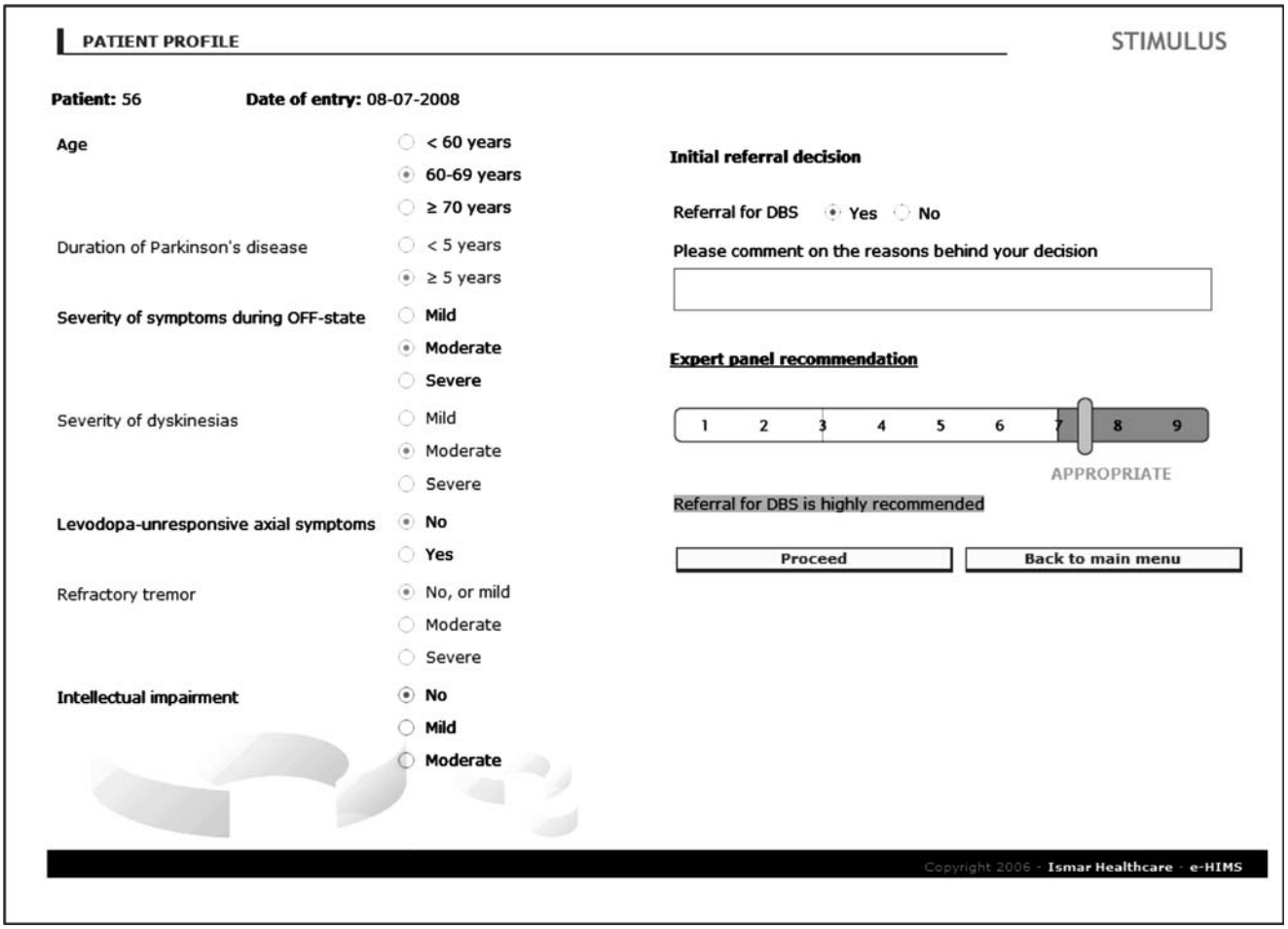

Fig. 1 User interface of the decision support tool

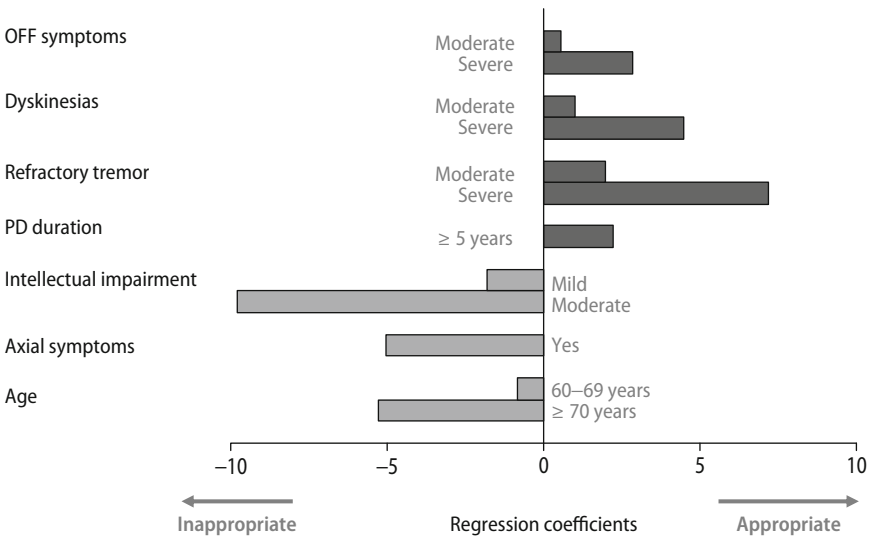

Fig. 2 Factors determining the panel judgement that referral is appropriate; results of logistic regression analysis

tial impact on the patient's quality of life. Similar considerations led to a pragmatic description for responsiveness to levodopa. Pre-operative levodopa-responsiveness has been proven to be an important predictor of treatment outcome [10, 12, 17, 23]. Such a levodopa challenge test is usually not feasible in general neurology practice, and the panel assumed that the general description chosen ('patient still has clear motor improvement with levodopa') is sufficiently discriminative as a minimum requirement for DBS consideration. The significance of physical and mental co-morbidities on the eligibility for DBS is heterogeneous and should be assessed by the DBS specialised centres. For that reason, the panel abstained from detailed descriptions and retained only clinical conditions that obviously form a contra-indication for (brain) surgery, and severe medically-refractory mental conditions that can jeopardise the outcome of or compliance with DBS treatment [22].

The seven variables with a relative contribution to the appropriateness of referral for DBS form the heart of the decision tool. The impact of symptoms during OFF-state, dyskinesias, and levodopa-unresponsive tremor on quality of life was divided over different variables, because the panel felt that this distinction could be relevant in combination with other patient characteristics. For example, in a patient with severe refractory tremor, shorter disease duration may be considered acceptable before considering DBS. For all symptoms, severity level was positively associated with the panel's judgment that referral is appropriate, with the category 'severe' showing the most pronounced impact (Fig. 2). Disease duration ≥ 5 years did also positively affect the appropriateness outcomes. This is largely to be ascribed to the fact that a period of 5 years is often considered needed to discriminate between idiopathic and non-idiopathic parkinsonism. However, studies have also suggested that the benefits from DBS are larger in patients with shorter disease duration [2, 17, 20, 23], which justified the choice of not including disease duration ≥ 5 years as an absolute criterion. The negative association between age and appropriateness of referral is in line with the results of studies that have suggested greater benefit of DBS in younger patients [17]. Nevertheless, as most clinical trials have excluded patients above the age of 70 or 75 years, little data is available on efficacy and safety of DBS in the elderly group. As a result, advanced chronological age by itself should not be considered an absolute exclusion criterion for DBS [12]. The strong tendency of the panel's opinion against referral in patients with levodopa-unresponsive axial symptoms obviously stems from the studies showing that these symptoms are unlikely to improve after DBS [3, 11, 12]. Severity of cognitive impairment showed a negative association with the appropriateness of referral. Although there is insufficient evidence that DBS may affect cognitive status in certain profiles [22], the results reflect the panel opinion that the outcome of DBS in patients who exhibit cognitive impairment may be less favourable due to a decreased ability to cooperate with the treatment and/or a risk of further neuropsychological deficit.

About one third of PD cases assessed were deemed appropriate for referral to consider DBS. It should be stressed that this proportion applies to a theoretical population, and that the distribution of patient profiles and related appropriateness figures (appropriate, inappropriate and uncertain) in a real-world setting are unknown. For that reason, an observational survey has recently been initiated, involving 40 movement disorder centres with expertise in DBS and 400 referral neurologists in several European countries and Canada. In this survey, referral neurologists are asked to use a web-based version of the decision tool to document patient profiles, referral decisions and follow-up data in consecutive patients with PD, seen in their practice for any routine consultation. We emphasise that the appropriateness ratings, though very consistent, reflect only the panel opinions on the likelihood that a patient may be a good candidate for DBS consideration. The final therapeutic decision will, of course, be the prerogative of the movement disorder centre. To draw definite conclusions about the predictive value of the decision tool, further research will be conducted to assess the relationship between the panel recommendations and final selection decisions on DBS by specialised centres.

Conflict of interest E. Moro received honoraria for lecturing and consulting services form.

N. Allert has received honoraria from myotronic for lecturing and consulting services.

J.-L. Houeto has received honoraria from meotronic for lectures and participation as an expert in the study.

H. Stoevelaar has received honoraria from meotronic for advice to the dyoxin of the study and data analysis.

T.-M. Phan was a former meotronic employee.

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