Psychiatric symptoms in patients with Parkinson disease presenting for deep brain stimulation surgery

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Object. Postoperative psychiatric symptoms have been associated with subthalamic deep brain stimulation (DBS) for Parkinson disease (PD), and preoperative psychiatric vulnerability, the effects of surgery, stimulation, medication changes, and psychosocial adjustment have been proposed as causative factors. The variables involved in whether preoperative psychiatric symptoms improve or worsen following surgery are not yet known. In the present study, preoperative psychiatric symptoms were systematically assessed in patients with PD presenting for routine preoperative psychiatric assessment.

Methods. Forty consecutive patients with PD presenting for DBS were interviewed using the Mini International Neuropsychiatric Inventory. Current depressive symptoms were quantified using clinician-and patient-rated depression scales. Seventy-eight percent of patients had at least one lifetime or current Axis I psychiatric diagnosis. The prevalence rates were comparable to or greater than those in the general population of patients with PD. Twenty-three percent of patients required psychiatric treatment for current symptoms prior to being considered eligible for DBS.

Conclusions. As part of the selection process for surgery, members of the study population were chosen for their lack of overt dementia or other active disabling psychiatric symptomatology. The incidence rates of psychiatric disorders, including those diseases occurring in the general population affected with PD, were greater than expected. Data in the present study lead one to question the reliability of patient-rated depression scales as the sole instrument for assessing depression. The authors highlight the need for evidence-based guidelines in the management of these preoperative symptoms as well as the involvement of psychiatric personnel in the assessment and management of these symptoms.

KEY WORDS • depression • anxiety • psychosis • Parkinson disease • subthalamic stimulation

Parkinson disease is a neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. Bilateral DBS targeting of the STN is a neurosurgical procedure used in treating advanced PD and significantly improves motor function, motor fluctuations, and levodopa-induced dyskinesias. Nevertheless, a variety of postoperative psychiatric symptoms have been reported following STN DBS surgery, ranging from stimulation-induced acute symptoms (mirthful laughter, mania, depressive states, aggression, and visual hallucinations) to delayed symptoms (euphoria, hypomania, depression, apathy, addictive behaviors, and relationship difficulties). The hypothesized causative factors include premorbid vulnerabilities, the effects of surgery, stimulation, medication changes, and psychosocial adjustment.

Psychiatric symptoms are a very common comorbidity in patients with PD. The role of premorbid psychiatric vulnerabilities in the pathophysiology of postoperative symptoms has not been completely clarified. Whether these preoperative disorders represent risk factors or may be improved either directly or indirectly by STN stimulation or by decreases in dopaminergic medications is as yet unknown. The importance of determining the appropriate management of these preoperative psychiatric disorders is commonly anecdotal noted; however, there is no literature on the prevalence of psychiatric disorders in patients with advanced PD presenting for STN stimulation.

The purpose of the present study was to determine the frequency of premorbid psychiatric disorders in patients with PD who presented for assessment prior to STN DBS.

Clinical Material and Methods

Patient Population

Forty consecutive patients with advanced PD were referred from the Morton and Gloria Shulman Movement Disorders Centre, Toronto Western Hospital, as part of the...
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Routine preoperative psychiatric assessment for STN DBS surgery and were assessed for lifetime and current psychiatric diagnoses. The catchment area for referrals consisted primarily of the province of Ontario; four patients were referred from outside the province. Patients were consecutive referrals for neurosurgical assessment between September 2002 and March 2004. Although these patients retained a good motor response to dopaminergic medications, their responses were complicated by refractory disabling motor fluctuations and dyskinesias. When initially considered as candidates for DBS, patients had been prescreened by their referring neurologists (primarily movement disorder neurologists) to rule out overt dementia or active disabling psychiatric symptoms. Patients did not routinely undergo psychiatric assessment prior to referral for consideration of surgery. The prescreened patients were referred to our movement disorders neurologist (E.M.) subspecializing in neurosurgical patients and were then referred for neuro-psychiatric and neuropsychological assessment if they were reasonable surgical candidates fulfilling CAPSIT-PD criteria and were interested in, and able to tolerate, surgery. The cohort included patients with potentially treatable psychiatric symptoms (identified by E.M.) who were otherwise good surgical candidates.

The characteristics of the patients are presented in Table 1. Four of 40 patients were excluded from surgery because of an advanced age (> 70 years).

Levodopa equivalents were estimated as follows: total levodopa equivalents = regular levodopa dose × 1 + levodopa continuous release dose × 0.75 + pramipexole dose × 67 + ropinirole dose × 16.67 + pergolide dose × 100 + bromocriptine dose × 10 + (regular levodopa dose + [levodopa continuous release dose × 0.75]) × 0.25 if taking tolcapone.*

Table 1: Characteristics of 40 patients with advanced PD presenting for DBS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>40</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>27/14</td>
</tr>
<tr>
<td>mean age at assessment (yrs)</td>
<td>55.6 ± 9.6</td>
</tr>
<tr>
<td>mean duration of disease (yrs)</td>
<td>11.7 ± 3.8</td>
</tr>
<tr>
<td>mean dosage of levodopa &amp;/or equivalent (mg/day)†</td>
<td>1105 ± 545.2</td>
</tr>
</tbody>
</table>

* Values are expressed as the means ± standard deviations.
† One patient was not taking dopaminergic medications because of an intolerance to the side effects. Ten patients were also taking amantadine (mean dosage 280 mg/day).

Patient Evaluation

Patients were evaluated using the MINI, a semistructured diagnostic interview based on the DSM-IV criteria, which elicits selected previous and current Axis I psychiatric disorders. The MINI is a shortened version of the semistructured diagnostic interview, the Structured Clinical Interview for DSM-IV. All symptoms were confirmed on a psychiatric interview conducted by the same psychiatrist, and corroborative collateral and caregiver information were obtained when available. In screening for comorbid disorders, we used a nonhierarchical approach to diagnosis; that is, a diagnosis was rendered if the patient fulfilled criteria for the disorder. The severity of past episodes was qualitatively assessed according to the duration of symptoms, need for intervention (change in medications, psychotropic medications, psychiatric assessment, suicidal or behavioral issues, and hospitalization), and response to intervention. Patients were assessed while on medications. The duration of each assessment was approximately 1 to 2 hours.

Current mood and anxiety disorders were diagnosed using the MINI. The severity of current depression was evaluated with the clinician-rated MADRS and the patient-rated BDI, whose psychometric properties have been investigated in patients with PD. Psychotic symptoms were specifically screened and reported as delusions, hallucinations (visual or auditory), or minor hallucinations (for example, shadows, presence hallucinations, and illusions). Dopamine dysregulation syndrome characterized by levodopa abuse; novelty-seeking behaviors, and secondary hypomania was specifically evaluated. Levodopa abuse was determined using the MINI. Dopaminergic medication was added to the screening list of nonalcoholic psychoactive substance use disorders. Behaviors including pathological gambling were also screened.

To decrease the possibility of underreporting due to a patient’s concerns regarding their psychiatric status, which could affect the assessment of surgical candidacy, to optimize the treating team’s ability to identify and actively manage any underlying symptoms, and to identify patients requiring active postoperative follow up, patients were instructed to be as frank as possible.

Results

Patient characteristics are reported in Table 1. Six patients (15%) had a total of three Axis I diagnoses, nine patients (23%) had two, and 16 patients (40%) had one. Thirty-one (78%) of 40 patients had at least one lifetime or current Axis I diagnosis. The results of the diagnostic assessments along with reported rates of psychiatric disorders in the literature on PD in general are presented in Table 2. Fifteen (38%) of 40 patients were considered to have an elevated risk of psychiatric disorder. Diagnoses among these patients included a history of medication-induced mania with psychosis (three patients), current depression contraindicating surgery (MADRS > 19; six patients), current active delusional symptoms (one patient), levodopa abuse (one patient), pathological gambling (one patient); clinically severe panic disorder unrelated to motor fluctuations (two patients), and a history of complicated depression (one patient). Twelve (30%) of 40 patients were relatively contraindicated for surgery pending psychiatric treatment because of, and per the CAPSIT-PD criteria, active depressive (MADRS > 19), manic, or delusional symptoms; uncontrolled levodopa abuse; pathological gambling; or severe panic symptoms. Three of these 12 patients were excluded from STN stimulation surgery because of cognitive impairment.

The mean rating scale scores of the depressed (DSM-IV
TABLE 2
Current and lifetime psychiatric disorders in 40 patients with PD presenting for DBS and in those reported on in the PD literature*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients (%)</th>
<th>Prevalence Rates in PD Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>major depression (treated w/ antidepressants)</td>
<td>24 (60) 45–85</td>
<td>40–501, 2.7–19.6†</td>
</tr>
<tr>
<td>dysthymia</td>
<td>11 (28) 14–42</td>
<td>Cummings, 1992; Kostic, et al., 2003</td>
</tr>
<tr>
<td>depression w/ comorbid anxiety</td>
<td>8 (20) 8–32</td>
<td></td>
</tr>
<tr>
<td>current depression (MADRS &gt;19)</td>
<td>6 (15) 4–26</td>
<td></td>
</tr>
<tr>
<td>suicide attempts</td>
<td>2 (5) NA</td>
<td>1.5 Molho, et al., 2002</td>
</tr>
<tr>
<td>medication-induced delusions or hallucinations</td>
<td>14 (35) 20–50</td>
<td>16–26 Fenelon, et al., 2000; Molho, et al., 2002</td>
</tr>
<tr>
<td>medication-induced visual hallucinations§</td>
<td>11 (28) 14–42</td>
<td>40 Richard &amp; Kurlan, 2002</td>
</tr>
<tr>
<td>panic attacks, GAD, or social phobia</td>
<td>16 (40) 25–55</td>
<td></td>
</tr>
<tr>
<td>panic attacks§</td>
<td>12 (30) 16–46</td>
<td></td>
</tr>
<tr>
<td>panic disorder</td>
<td>4 (10) 1–19</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>6 (15) 4–26</td>
<td></td>
</tr>
<tr>
<td>secondary social phobia</td>
<td>7 (18) 6–30</td>
<td></td>
</tr>
<tr>
<td>substance or levodopa abuse</td>
<td>2 (5) 2–13</td>
<td></td>
</tr>
<tr>
<td>pathological gambling</td>
<td>1 (3) 2–8</td>
<td></td>
</tr>
</tbody>
</table>

* GAD = generalized anxiety disorder; NA = not applicable.
† Mean prevalence rate in tertiary referral cohort studies.
‡ Range of prevalence rates of major depression in community-based cohort studies.
§ Including “benign” visual hallucinations.
|| Not confined to motor “off” periods.

Discussion

In the present investigation 40 consecutive patients with advanced PD who had been referred to our service as part of the routine preoperative psychiatric assessment for STN DBS surgery were assessed for lifetime and current psychiatric diagnoses. As part of the selection process for surgical candidacy, the study population would routinely have been prescreened by referring neurologists for the absence of dementia or active disabling psychiatric symptomatology. Our results highlight the high psychiatric burden in this popula-
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### TABLE 3

Mean depression and anxiety scores in depressed compared with nondepressed patients with PD presenting for DBS*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Mean Score</th>
<th>95% CI</th>
<th>Mean Score</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>depressed†</td>
<td>19.2 ± 4.8</td>
<td>16.4–22.1</td>
<td>18.0 ± 10.9</td>
<td>11.3–24.8†</td>
</tr>
<tr>
<td>nondepressed</td>
<td>8.4 ± 5.2</td>
<td>6.5–10.4‡</td>
<td>9.9 ± 5.9</td>
<td>7.7–12.1</td>
</tr>
</tbody>
</table>

| p value       | <0.0001    | 0.0026  |

* Results are expressed as the means ± standard deviations.
† Defined by DSM IV criteria.
‡ One patient not scored because of language barrier.
§ One patient not scored because of current manic episode.
|| Two patients not scored because of language barrier.

A statistically significant difference was noted in the clinician-rated MADRS and patient-rated BDI scores between depressed (DSM-IV diagnosis) and nondepressed patients. Two patients, however, with diagnoses of moderately severe depression (MADRS > 19) had very low scores (that is, 5) on the patient-rated BDI. The limitations in the reliability of this latter scale were reflected in the extended CIs and may be a result of limited insight into, or denial of, psychiatric symptoms or their minimization because of concerns regarding surgical eligibility. This finding raises the question of the reliability of patient-rated depression rating scales as the sole instrument for assessing depression.

The prevalence of medication-induced mania in our study may be elevated in comparison to that in the general PD population given the context of a cohort having advanced PD with an onset at a relatively young age together with the use of multiple medications and high levodopa dosage equivalents. The prevalences of depression, medication-induced psychotic symptoms, and anxiety disorders were either similar to, or greater than, those in the general PD population.

In the present study at least one previous or current Axis I psychiatric disorder was diagnosed in 78% of patients; at least three separate disorders were diagnosed in 15%. Notably, the Axis I diagnoses do not capture the full range of symptoms reported in the PD literature including the extent of psychiatric symptoms, apathy, hypersexuality, and mood fluctuations.

Surgery was relatively contraindicated in 12 (30%) of 40 patients, pending psychiatric treatment because of active depression (MADRS > 19), manic, or delusional symptoms; uncontrolled levodopa abuse; pathological gambling; or severe panic symptoms. Determination of a psychiatric risk was based on the CAPSIT-PD criteria, previous reports of postoperative exacerbation in patients with these symptoms, or the likelihood of difficulties in tolerating the surgical procedure given the severity of active symptoms on presentation. Whether patients with medication-induced symptoms (for example, pathological gambling, mania, or hallucinations) might improve following surgery has not yet been determined. Whether the cutoff for the CAPSIT-PD criteria is appropriate is not known. Authors of two previous studies on the role of preoperative depression in postoperative depression outcomes had contradictory conclusions. Data in recent literature indicate that the CAPSIT-PD criteria contraindicate surgery in patients with moderate depression is overly stringent. For instance, in one study, patients with moderately severe depression at the time of surgery did not have elevated depression rating scores at the 1st postoperative year follow up. Three years after surgery, 14% of these patients had worsened depression scores and 86% had improved scores. In contrast, 50% of patients with severe depression at the time of surgery had severe depression 3 years after surgery. Note, however, that the authors of this study did not report the premorbid history of depression or use of antidepressants, which may play a role in the recurrence of depression. Neither did they...
report on the presence of depression or the need for treatment with antidepressants between the times of assessment. Furthermore, whether effective psychiatric treatment prior to surgery and prophylactic antidepressants (which are well-established methods of decreasing the risk of depression relapse according to the general psychiatric literature) change the outcomes in patients with severe depression at the time of surgery is not known. Whether preoperative treatment of these psychiatric disorders changes outcome in general is also not known and needs further careful study.

Three of the 12 patients in whom surgery was contraindicated were excluded from STN DBS because of cognitive impairment. Given the lack of guidelines and ambiguity in the literature as well as the lack of evidence concerning patients whose psychiatric symptoms had been adequately treated preoperatively, the remaining nine patients were considered appropriate for surgery following effective psychiatric treatment. Two patients with a history of attempted suicide were carefully evaluated and their attempts were considered to be a low risk.

Eight of 11 patients have since undergone surgery and have at least 3 months of available postoperative data. The remaining three patients have either recently undergone, or are awaiting, surgery. Postoperative data were obtained from an uncontrolled series and were based on a small cohort with varying diagnoses, and the follow up was of variable and limited duration. Furthermore, the data have not been analyzed with respect to electrode placement, degree or rate of change of medications, or psychosocial factors. The frequency of postoperative psychiatric outcomes among these series will also be elevated as these patients have been closely observed; a control group similarly followed up would be required to determine if the frequency is different from that in the general PD population undergoing STN DBS. Thus, the data cannot be considered indicative of the role of preoperative vulnerability in postoperative psychiatric outcomes and are too limited to be generalizable. Nevertheless, the preliminary data indicate that preoperative medication-induced mania, consistent with previous observations of hypomania, may be associated with transient postoperative mania within the early postoperative period, which responds to the usual treatments. Effectively treated moderate to severe depression was associated with postoperative depression in one of four patients; postoperative depression was also responsive to treatment. A previous suicide attempt screened appropriately for degree of severity is not necessarily a contraindication for surgery. The postoperative psychiatric symptoms have all been transient and manageable. In addition to preoperative psychiatric intervention, these patients require close postoperative psychiatric follow up.

Conclusions

We reported the results of a systematic psychiatric assessment of lifetime and current psychiatric diagnoses in 40 consecutive patients with advanced PD who had presented for assessment for STN DBS surgery and highlighted the high burden of psychiatric disorders in this population. Notably, which preoperative symptoms improve either directly or indirectly due to STN stimulation or decreases in dopaminergic medications and which patients are at risk for decompensation and require preoperative psychiatric intervention is not yet known. Furthermore, there is insufficient evidence in the literature to determine whether the current presence or severity of preoperative psychiatric symptoms or a previous history of psychiatric disorders should be used as contraindications for surgery. Severe depression at the time of assessment for surgery should be considered as a relative contraindication pending the disorder’s successful treatment. Note that psychiatric disorders, in contrast to cognitive deficits, are potentially reversible and treatable. We emphasize the need for large-scale prospective studies to investigate risk factors associated with postoperative psychiatric symptoms, for evidence-based guidelines for the treatment of patients with these symptoms, and for involvement of psychiatric personnel in the treatment of these patients.

References

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