Deep brain stimulation for Huntington’s disease: long-term results of a prospective open-label study

Clinical article

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Object. To date, experience of globus pallidus internus (GPi) deep brain stimulation (DBS) in the treatment of Huntington’s disease (HD) has been limited to a small number of case reports. The aim of this study was to analyze long-term motor outcome of a cohort of HD patients treated with GPi DBS.

Methods. Seven patients with pharmacologically resistant chorea and functional impairment were included in a prospective open-label study from 2008 to 2011. The main outcome measure was the motor section of the Unified Huntington’s Disease Rating Scale. The primary end point was reduction of chorea.

Results. Patients underwent MRI-guided bilateral GPi implantation. The median duration of follow-up was 3 years. A significant reduction of chorea was observed in all patients, with sustained therapeutic effect; the mean improvement on the chorea subscore was 58.34% at the 12-month follow-up visit (p = 0.018) and 59.8% at the 3-year visit (p = 0.040). Bradykinesia and dystonia showed a nonsignificant trend toward progressive worsening related to disease evolution and partly to DBS. The frequency of stimulation was 130 Hz for all patients. DBS-induced bradykinesia was managed by pulse-width reduction or bipolar settings. Levodopa mildly improved bradykinesia in 4 patients. Regular off-stimulation tests confirmed a persistent therapeutic effect of DBS on chorea.

Conclusions. GPi DBS may provide sustained chorea improvement in selected HD patients with pharmacologically resistant chorea, with transient benefit in physical aspects of quality of life before progression of behavioral and cognitive disorders. DBS therapy did not improve dystonia or bradykinesia. Further studies including quality of life measures are needed to evaluate the impact of DBS in the long-term outcome of HD.

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Key Words • Huntington’s disease • deep brain stimulation • chorea • globus pallidus internus • bradykinesia • functional neurosurgery

Huntington’s disease (HD) is a devastating neurodegenerative disorder characterized by progressive cognitive impairment, movement disorders, and psychiatric symptoms. Despite remarkable progress in the understanding of the pathogenesis of this disease, disease-modifying strategies are not yet available.

Several pharmacological treatments have been proposed, leading to partial relief of movement disorders and behavioral symptoms, but only a small number of randomized clinical trials have been conducted.

Functional neurosurgical techniques (including pallidotomy and thalamotomy) have been used in the past to treat chorea in probable HD. To date, there are limited data on the efficacy of globus pallidus internus (GPi) deep brain stimulation (DBS) in HD. Only 6 case reports have been published, all of them demonstrating an improvement in chorea. Prospective studies are needed to establish the impact of DBS on the evolution of this progressive disease. Little is known about long-term effects.
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of this therapy: only 2 studies have reported results of DBS treatment with more than 12 months of follow-up.2,26 We describe the long-term outcome for 7 consecutive patients treated with bilateral GPi DBS.

Methods

Design

Seven patients were followed prospectively in an open-label pilot study from January 2008 to December 2011.

Inclusion criteria were as follows: 1) genetically confirmed HD with chorea unresponsive or poorly responsive to medical treatment (including tetrabenazine or another drug [a benzodiazepine]); 2) functional impairment defined as Unified Huntington’s Disease Rating Scale (UHDRS) Independence Scale score ≤ 70, and Total Functional Capacity (TFC) score ≤ 8; 3) no severe cognitive impairment, as demonstrated by preserved language skills (patients included in the study had different degrees of dysexecutive syndrome, no established cutoff scores were defined in global neuropsychological tests); and 4) support of a reliable caregiver (mandatory). Exclusion criteria were: 1) history of self-injurious behavior or unstable psychiatric comorbidities, or 2) contraindications to MRI or anesthesia.

Surgery

All patients underwent MRI-guided bilateral GPi implantation of quadripolar electrodes (Model 3389, Medtronic). Stereotactic surgery (using a Leksell frame) was performed under general anesthesia without micro-electrode recordings, by direct targeting. Details of the surgical procedure can be found elsewhere.3 Within the same anesthetic procedure, all patients underwent postoperative MRI (to check electrode position) followed by surgical placement of an implantable pulse generator (IPG) (Soletra or Kinetra [Medtronic]). Both MRI acquisitions were done with a 1.5-T scanner. The IPG system was positioned abdominally in 6 patients, and the other patient underwent submammary implantation.

Main Outcome Measures

The main outcome measure was the motor section of the UHDRS,24 with total chorea score reduction as the primary end point. “Finger taps,” “pronate/supinate hand,” and “global body bradykinesia” items were grouped in a common “bradykinesia subscore” in this study. Patients were regularly videotaped with the DBS unit switched on and with it switched off. Clinical assessment was not blinded to DBS condition. Off-stimulation tests were programmed in the follow-up to assess clinical response and disease progression.

Neuropsychological assessment used the Mattis Dementia Rating Scale (DRS) as a measure of global cognitive functioning. Analysis of cognitive aspects is beyond the scope of this study. DBS programming was performed at each clinical visit by the neurologist.

DBS Programming

The initial settings were as follows: monopolar stimulation (plot 1 negative), 130-Hz frequency and 0.5 V, with progressive adjustment of the amplitude thereafter. Different pulse widths were used according to the clinical response and DBS-related adverse events. Bipolar stimulation was tried whenever the patient did not tolerate high levels of stimulation in monopolar mode.

Ethics

The patients and their families were informed about the aims of the study, potential risks and side effects of the surgical procedure, the follow-up (including progressive adjustment of stimulation settings, and the need for IPG system replacement), and our team’s previous experience with DBS in movement disorders. Informed written consent was obtained for all patients.

Statistical Analysis

Preoperative and postoperative absolute scores on the UHDRS were calculated, together with the amount of improvement ([preoperative score–postoperative score]/preoperative score) × 100. Due to the small size of the sample and the non-normality of the distributions, preoperative and postoperative scores were compared by means of the nonparametric Wilcoxon rank-sum test. The software STATISTICA (StatSoft version 9.1) was used for analysis.

Results

Baseline and Demographic Characteristics

Seven consecutive patients with HD (mean age 49.71 ± 19.41 years) underwent surgery for bilateral GPi DBS in our center between January 2008 and November 2010. The patients’ demographic characteristics are summarized in Table 1. The mean duration of symptomatic motor disease before surgery was 4.86 ± 2.27 years. The mean CAG repeats length was 45.29 ± 4.5. Patients were followed up until the end of 2011. The median length of follow-up was 3 years.

Chorea was poorly responsive to different pharmacological tests performed before surgery (Table 1). Tetrabenazine had been tested in 71.43% of the patients with partial clinical response; the patients in Cases 2 and 5 did not tolerate this drug. Different neuroleptics had also been tried before surgery, with only partial efficacy, in 85.71% of the patients. Other drugs frequently used by these patients were benzodiazepines (42.86%), antidepressants (71.43%), and valproate (28.57%).

UHDRS Motor and Functional Scores

The mean values for UHDRS subscores are shown in Table 2. Changes in the individual patients’ UHDRS total motor scores and chorea subscores over time are shown in Figs. 1 and 2, respectively. Despite a mean initial improvement of 10.91% in UHDRS total motor score at the 12-month follow-up visit (p = 0.090), there was a nonsignificant trend towards worsening in further visits.
### TABLE 1: Demographic data, drug therapy changes, and individual off-DBS test results*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Disease Duration (yrs)†</th>
<th>CAG Repeats Length</th>
<th>Preop Pharmacol Tx</th>
<th>Date of Surgery</th>
<th>Drug Changes After Surgery</th>
<th>Pharmacol Tx at Last Study Visit</th>
<th>% Change at Last FU Visit Off-DBS Test</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>78, F</td>
<td>5</td>
<td>40</td>
<td>tetrabenazine, tianeptine</td>
<td>2008</td>
<td>tetrabenazine withdrawn (2008)</td>
<td>levodopa (2008), paroxetine, alprazolam</td>
<td>ΔC: 50% ΔD: 0%</td>
</tr>
<tr>
<td>2</td>
<td>39, M</td>
<td>8</td>
<td>47</td>
<td>pipotiazine, clonazepam, valproate</td>
<td>2008</td>
<td>pipotiazine reduced (2008)</td>
<td>levodopa (2008), cyamemazine (2010), valproate, pipotiazine</td>
<td>ΔC: 77.3% ΔD: 0%</td>
</tr>
<tr>
<td>4</td>
<td>54, M</td>
<td>8</td>
<td>42</td>
<td>olanzapine, buspirone, valproate, escitalopram</td>
<td>2008</td>
<td>olanzapine increased (2009) due to behavior disorder</td>
<td>olanzapine, alprazolam, valproate, paroxetine</td>
<td>ΔC: 68.4% ΔD: −21.4%</td>
</tr>
<tr>
<td>6</td>
<td>30, M</td>
<td>3</td>
<td>50</td>
<td>tetrabenazine</td>
<td>2010</td>
<td></td>
<td>olanzapine, venlafaxine, alprazolam, clonazepam, tetrabenazine</td>
<td>ΔC: 57.1% ΔD: 33.3%</td>
</tr>
<tr>
<td>7</td>
<td>36, F</td>
<td>3</td>
<td>48</td>
<td>olanzapine, paroxetine, tetrabenazine</td>
<td>2010</td>
<td>tetrabenazine withdrawn (2010)</td>
<td>olanzapine increased (2011), venlafaxine, alprazolam, clonazepam, tetrabenazine, zopiclone, hydroxyzine</td>
<td>ΔC: 30% ΔD: 0%</td>
</tr>
</tbody>
</table>

* Off-stimulation tests for DBS were programmed in on-medication condition. The years in parentheses refer to the timing of drug therapy changes. FU = follow-up; pharmacol = pharmacological; Tx = treatment; w/drawn = withdrawn; ΔC or ΔD = % change in chorea or dystonia score: [(off-DBS score − on-DBS score/off-DBS score) × 100].

† Motor signs.

### TABLE 2: Longitudinal evolution of clinical parameters: UHDRS motor section, UHDRS functional scores, and Mattis Dementia Rating Scale*

| UHDRS Subscores† | Preop 4 Mos Postop 6 Mos Postop 1 Yr Postop 2 Yrs Postop 3 Yrs Postop |
|------------------|-----------------|----------------|----------------|----------------|----------------|
| chorea           | 17.0 (4.65)     | 8.29 (4.92)‡  | 9.6 (3.71)‡   | 7.14 (3.62)‡  | 7.0 (4.06)     | 7.0 (3.39)‡   |
| dystonia         | 4.14 (4.06)     | 2.86 (2.79)   | 4.6 (3.51)    | 6.14 (2.61)   | 7.2 (4.15)     | 8.6 (3.91)    |
| bradykinesia     | 7.43 (3.46)     | 8.29 (2.93)   | 8.4 (2.70)    | 7.57 (2.51)   | 13.2 (3.35)    | 12.6 (3.44)   |
| rigidity         | 1.14 (1.57)     | 1.14 (0.90)   | 1.8 (1.09)    | 1.86 (1.46)   | 2.6 (1.52)     | 2.4 (0.89)    |
| speech/orolingual| 2.57 (1.81)     | 2.43 (2.07)   | 2.8 (1.64)    | 2.43 (1.81)   | 4.0 (2.45)     | 4.4 (2.70)    |
| ocular movements | 9.29 (6.73)     | 8.86 (6.74)   | 14.3 (3.85)   | 10.29 (6.50)  | 13.4 (4.5)     | 15.0 (2.83)   |
| gait/steadiness  | 5.0 (2.94)      | 3.86 (3.02)   | 4.6 (2.88)    | 3.57 (3.50)   | 6.2 (2.59)     | 6.2 (3.27)    |
| Luria            | 2.0 (1.73)      | 2.0 (1.63)    | 2.6 (1.52)    | 2.0 (1.64)    | 2.6 (1.52)     | 2.4 (1.34)    |
| total UHDRS      | 48.7 (18.35)    | 36.9 (17.08)‡ | 49.4 (7.09)‡  | 41.43 (14.6)  | 56.6 (13.69)   | 58.8 (12.93)  |
| IS               | 62.9 (12.54)    | NA            | 64.3 (9.76)   | 64.3 (9.76)   | 56.0 (11.4)    | 50.0 (18.71)  |
| FA               | 13.3 (3.95)     | NA            | 13.0 (5.23)   | 13.3 (6.18)   | 8.2 (4.32)     | 7.0 (4.36)    |
| TFC              | 5.14 (2.34)     | NA            | 5.14 (2.34)   | 5.0 (2.58)    | 3.6 (2.30)     | 3.0 (2.23)    |
| Mattis DRS       | 112.5 (24.84)   | 116.86 (17.9) | 102.33 (17.6) | 89.4 (49.78)  |

* Values represent means (SD). FA = Functional Assessment; IS = Independence Scale; NA = not available; TFC = Total Functional Capacity.

† Maximum score for each item: chorea, 28; dystonia, 20; bradykinesia, 20; rigidity, 8; speech/orolingual, 8; ocular movements, 12; gait/steadiness, 8; Luria, 4; total UHDRS (motor section), 124; IS, 100; FA, 25; TFC, 13; Mattis DRS, 144.

‡ p value < 0.05 for comparison of preoperative vs postoperative scores (Wilcoxon rank-sum test).
Chorea. Compared with baseline, the UHDRS chorea subscore was significantly decreased 1 year after surgery (p = 0.018), with a mean improvement of 58.34% (SD 13.12%). The therapeutic effect was already evident at the 3-month follow-up visit. This reduction of chorea was sustained during the whole study period, with an average improvement of 59.8% (SD 22.86%) at the last study visit (p = 0.04).

The patients exhibited a significant reduction of chorea in several areas of the body: orolingual (64.61%) and
upper limbs (63.69%), followed by trunk (58.85%) and lower limbs (53.75%). Drug therapy (neuroleptics, tetrabenazine) was reduced or withdrawn following surgery in 5 patients.

Bradykinesia and Rigidity. An increase in bradykinesia was evident on longitudinal follow-up and was partially dependent on stimulation settings (greater increase with higher current drain). Pulse-width reduction allowed progressive adjustment of current density during the first months after surgery resulting in diminished bradykinesia, while the effect on chorea was maintained. The mean rigidity subscores did not differ significantly during follow-up.

In 2 cases (Cases 1 and 3), freezing of gait was observed in the first weeks after stimulation therapy was started. This symptom was partially controlled by adjustment of DBS settings after reduction of current density and change to bipolar stimulation.

Dystonia. There was a progressive nonsignificant trend toward worsening of dystonia (48.31% at 12 months of follow-up), which continued to increase up to the last examination. Interestingly, dystonia increased mainly in the upper limbs. Three patients developed progressive oromandibular dystonia, causing speech and swallowing worsening for two of them after 2 years of follow-up. The patient in Case 2 was treated with botulinum toxin injections with transient improvement in swallowing (sustained 1 year). Gastrostomy feeding was required for this patient (37 months after surgery) due to weight loss.

Neuropsychological Tests. Comparison between the preoperative Mattis DRS score and the score obtained 1 year after surgery did not show a statistically significant difference (p = 0.67). Despite progressive cognitive decline observed during the study (Table 2), the DRS score at last follow-up visit was not significantly different from the preoperative score. The patients in Cases 2 and 4 exhibited a more rapid decline after 2 years of follow-up, concomitant with progression of behavior disorder (and subsequent neuroleptic treatment).

Functional Outcome. After temporary stability, a nonsignificant trend toward functional decline as measured by Functional Assessment (FA), Independence Scale (IS), and Total Functional Capacity (TFC) scores began after the 2nd year of follow-up (Table 2).

Worsening in functional scores followed progression of behavior disorder and cognitive impairment in Cases 2, 4, and 7. Three patients (Cases 1, 2, and 4) were dependent for dressing and bathing at the last follow-up visit (2 of them were already partially dependent before surgery). DBS improved swallowing disorders secondary to chorea in 5 patients (Cases 2–5 and 7). Six patients maintained independence in eating or required only minimal assistance. Gait was preserved for all patients by the end of the study. The patients in Cases 1 and 3 were able to walk only with assistance; the patients in Cases 2 and 4 required only verbal supervision from one person, without physical contact. 3 years after surgery; the other 3 patients were able to walk independently. The patients in Cases 1 and 2 were institutionalized by the end of the follow-up (the patient in Case 1 was admitted to a chronic care facility for social reasons early after surgery). Care was provided at home for the rest of the group. The patients in Cases 5 and 6 could stay at home and supervise their children with help. The patient in Case 6 returned to work in part-time employment adapted for disabled people some months after surgery.

Levodopa Therapy

Four patients received adjuvant chronic treatment with levodopa (mean dose 287.5 ± 75 mg/day). There were no significant changes in rigidity, dystonia, or gait scores before and after the introduction of levodopa, and only a trend toward mild improvement of bradykinesia (mean reduction of 2.75 ± 0.96 points in a 6-month period, p = 0.07). A levodopa challenge test was performed for 5 patients without any significant clinical change: there was a mild reduction of rigidity for 2 patients and mild worsening of chorea in another 2. The patient in Case 4 did not tolerate levodopa (withdrawn after a 2-month trial) due to psychiatric adverse effects (aggressive behavior).

Other Pharmacological Treatments

Behavior disorders resulted in neuroleptic dose increase or introduction of neuroleptic therapy during the follow-up period in 4 patients (Table 1). Antidepressants were also necessary in several patients. Valproate improved aggressive behavior in two patients. After initial withdrawal, tetrabenazine was tested once again for the patient in Case 7 due to dystonic spasms in the lower limbs, but had only mild therapeutic effect.

Off-Stimulation Tests (Discontinuation of DBS Therapy)

All patients underwent off-stimulation tests within the first 18 months and at last follow-up visit, without interruption of pharmacological therapy. The chorea subscore was significantly different in off- and on-stimulation conditions at the last follow-up visit (p = 0.018), while there was no significant difference in dystonia scores (Table 1). The patients in Cases 2 and 4 exhibited immediate recurrence of severe generalized chorea, unsteadiness, and swallowing difficulties, following the off-stimulation test. This rapid clinical worsening was still present for both patients during the off-stimulation test at the last follow-up visit.

The clinical response to this test evolved over time for the patient in Case 5 from progressive worsening of chorea (off-stimulation test 12 months after surgery) to immediate and severe generalized chorea at the last visit (3 years after surgery). The other 4 patients had a slower pattern of worsening (with worsening occurring between 3 and 24 hours after stimulation was turned off).

Surgery and Complications

Despite cerebral atrophy, MRI-guided targeting showed good surgical accuracy when comparing preoperative and postoperative stereotactic MRI studies (mean targeting errors for the x coordinates: 0.7 ± 0.24 mm for the right side, 0.63 ± 0.26 mm for the left; mean targeting errors for the y coordinates: 0.64 ± 0.26 mm for the right, 0.56 ± 0.37 mm for the left side). There were no hemorrhagic complications.
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Hardware dysfunction (abnormal impedances, without fracture on radiographs) justified extension replacement after 13 months of follow-up in Case 4.

The patient in Case 5 required repositioning of one of the leads after 1 year due to suboptimal control of chorea. Following an episode of intolerance to frustration, one patient committed self-defenestration from a second floor without experiencing corporeal damage.

Stimulation Settings
Stimulation settings are summarized in Table 3. DBS-induced bradykinesia was managed by pulse-width reduction (in all 7 patients) and/or bipolar settings (in 5 patients). Shortened pulse width (from 450 μsec to 90–270 μsec) allowed progressive adjustment of current density, diminishing hypokinetic signs while maintaining the effect on chorea. The stimulation frequency was 130 Hz in all cases. Low-frequency (40-Hz) stimulation was tested in 2 patients without reduction in bradykinesia.

Discussion
Since the first description of GPi DBS treatment for patients with HD by Moro et al.,

28 4 other case reports4,9,17,26,28,39 have been published, all of them highlighting marked improvement of chorea and variable response in other movement disorders.

Our study provides a perspective on long-term outcome of DBS therapy in HD: as far as we know, this prospective study has the longest follow-up reported in literature.

The most important finding of this study was a sustained improvement of chorea over time despite the expected neurodegenerative progression. It could be argued that chorea reduction is a consequence of the natural history of the disease, not a clinical effect of DBS. However, discontinuation of DBS at the last follow-up visit induced reemergence of chorea, supporting a therapeutic effect. Kang et al.29 have also reported sustained chorea reduction 2 years after surgery in 2 patients with HD.

Although direct comparison with pharmacological clinical trials is not possible due to differences in study design, the therapeutic effect of DBS should be interpreted in light of other available treatment strategies for chorea in HD. Open-label extension of the first randomized, double-blinded, placebo-controlled study to test tetrabenazine confirmed a sustained effect on chorea over the course of 80 weeks with a mean reduction of chorea score of 4.6 points (representing a 30.87% improvement).10,23

Interestingly, we observed 2 different profiles of recurrence of chorea following interruption of DBS, with one group of patients exhibiting immediate and severe worsening of dyskinesias, and another group showing a slower pattern of worsening progressing between 3 and 72 hours after cessation of stimulation. This motor behavior resulting from discontinuation of DBS evokes the clinical findings previously described for the phasic component in primary generalized dystonia.6,14–16

The main limiting adverse effect encountered in our study was bradykinesia. Moderate bradykinesia and rigidity were already present in the preoperative clinical work-up, but there was evidence to support DBS-induced reversible bradykinesia associated with stimulation settings with a higher current drain. The causative role of high-frequency stimulation suggested by earlier studies9,28 could not be confirmed: low-frequency testing performed in 2 patients did not improve bradykinesia, supporting the lack of response reported by 2 other teams.17,26

Adjuvant levodopa treatment resulted in a trend toward mild reduction of bradykinesia in 4 patients. Levodopa has been used in the past to treat the hypokinetic-

<table>
<thead>
<tr>
<th>TABLE 3: Stimulation settings at last follow-up visit*</th>
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<tbody>
<tr>
<td><strong>Case No.</strong> Frequency (Hz)</td>
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<td>-----------------------------</td>
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<td>1</td>
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<tr>
<td></td>
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<td>7</td>
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</table>

* Neurostimulators (all from Medtronic) were as follows: Cases 2, 3, and 5, Soleta; Cases 1, 6, and 7, Kineta; Case 4, Activa PC.

The patients in Cases 3, 4, and 5 needed neurostimulator replacement before the end of the study, and in Case 4, an Activa PC unit was used.
rigid Westphal-variant of HD. Bradykinesia in HD is believed to result from progressive neuronal loss involving direct-pathway striatal neurons in advanced-stage disease. Secondary nigrostriatal dopaminergic denervation might contribute to this phenomenon in later stages.

Initial reports showed axial symptoms and gait deterioration after 10–11 months of follow-up. One of the patients reported on by Kang et al. exhibited progressive decline in dystonia, bradykinesia, and gait scores. In our study, gradual adjustment of stimulation settings with disease progression and levodopa treatment contributed to improve freezing of gait in 2 patients. Gait was possible for all patients by the end of the study, but 2 of them could only walk with assistance.

Functional improvement in HD does not depend only on relief of motor symptoms: progressive cognitive impairment and apathy are also substantial factors leading to disability. Depressive symptoms, total functional capacity, and cognitive performance have been identified as the most important factors determining health-related quality of life (HR-QoL). Although the role of motor symptoms was secondary, UHDRS Total Motor Score was significantly correlated with the physical dimension of generic HR-QoL scales (SF-36) and Sickness Impact Profile.

Ho et al. showed that the impact of HD was perceived differently by patients depending on the clinical stage of the disease (defined according to the Shoulson and Fahn severity scale classification). Pauelsen et al. found that depression was more prevalent in earlier stages of the disease (mainly at Stage 2, TFC: 7–10). The Huntington’s disease HR-QoL questionnaire (HDQoL) showed a gradual decline with disease evolution in the “Physical and functional” specific scale (including gait, balance, dressing, eating, swallowing, independence, and so forth) with lower scores at advanced stages (Stages 4 and 5, TFC: 0–2).

In the absence of specific measures of HR-QoL, our study cannot prove directly whether reduction of chorea in this group of patients was associated with an improvement of quality of life. Nevertheless, indirect data concerning motor and functional aspects of quality of life can be inferred from our results.

Functional outcome measures (TFC, IS, FA) exhibited a nonsignificant trend toward progressive worsening over the course of the study. However, most of the patients were in a moderate stage of HD, with a mean TFC corresponding to Stage 3 in the Shoulson and Fahn classification, and the clinical stage remained unchanged for the group over the course of the study. Care could be provided at home for most of the patients: only 2 patients required institutionalization. Motor symptoms (marked chorea, bradykinesia, and impaired gait and balance), rather than psychiatric symptoms, have been shown to be predictors of nursing home placement in HD.

Reduction of chorea diminished swallowing disorder and facilitated nursing care in advanced stages of the disease.

Furthermore, in our study, DBS allowed initial neuroleptic dose reduction or discontinuation, with a possible influence on cognitive performance. Global cognitive function, as measured by the Mattis DRS, did not show significant decline 1 year after surgery, suggesting safety of pallidal DBS in this context.

A multidisciplinary approach, with systematic psychiatric and neuropsychological evaluation, is essential to identify factors associated with more rapid cognitive and behavioral deterioration, particularly within the group of younger patients.

Ethical considerations support selection of patients with preserved communication and reasoning skills.

The main limitation of this study is that clinical assessment was not blinded to DBS condition. Programmed off-stimulation tests were not associated with discontinuation of pharmacological treatment, which would have allowed a better appraisal of disease progression. Although neuroleptic treatment may interfere with interpretation of clinical response, the efficacy of DBS therapy on chorea is supported by the results observed in off-stimulation/on-medication tests.

Another important limitation of this study was the lack of prospective assessment of quality of life with a disease-specific validated scale. Given the inexorable course of this degenerative disease, this last issue should be the main end point of future studies analyzing the role of DBS in HD. Given the current lack of neuroprotective therapies, we believe that symptomatic treatment with GPi DBS may provide comfort and improve physical aspects of quality of life for selected patients in early-moderate stages of disease, with predominant chorea, before the disease has progressed to severe cognitive or psychiatric impairment.

Conclusions

In conclusion, GPi DBS should be considered as an alternative treatment in HD patients with prominent chorea that is poorly responsive to pharmacological therapy and causing functional impairment. Our results do not support the indication of DBS for HD clinical presentations dominated by dystonia or bradykinesia. The therapeutic effect of DBS on chorea was sustained over time for at least 3 years.

Further studies are needed to refine eligibility criteria for GPi DBS and to analyze the impact of this therapy on quality of life.

Acknowledgments

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Disclosure

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