

Abstract: Among 30 Parkinson's disease patients who received high frequency stimulation of the subthalamic nucleus, 5 developed remarkable disorders of mood or sexual behavior after the implant. We describe 2 men who developed mania and hypersexuality a few days after the implant that lasted for some months and then gradually disappeared spontaneously. © 2002 Movement Disorder Society

Key words: high frequency stimulation; Parkinson's disease; subthalamic nucleus; UPDRS

High frequency stimulation (HFS) of the subthalamic nucleus (STN) markedly improves the motor symptoms of Parkinson's disease (PD) and reduces the requirement for dopaminergic therapy.¹⁻³ The possible neuropsychological and behavioral effects of this technique, however, have not been defined completely.^{4,5} Persistent or transient emotional states induced by HFS have been described recently in patients who received STN implants. A persistent depressive disorder unmodified by changes in stimulation settings was described in 4 PD patients who underwent bilateral STN HFS.⁶ Transient major depression was reported in a woman with PD when HFS was delivered to the left substantia nigra, 2 mm below the STN.⁶ By contrast, transient episodes of involuntary laughter were induced by STN stimulation in 2 men with PD.^{7,8} Similarly, a transient euphoric state with laughter, induced by high voltage stimulation, was reported in 2 PD patients who received bilateral STN HFS.⁶

Among the 30 PD patients treated successfully in the Gemelli hospital by bilateral STN HFS, 5 developed remarkable disorders of mood or sexual behavior after the implant. A 61-year-old man who had suffered from major depression after the death of his wife developed a transient euphoric state after the implant. A 57-year-old woman, with a history of hypomania during youth, experienced a marked increase of sexual drive, which gradually appeared in the first month after the implant, lasted for about 18 months, and then gradually disappeared. A 54-year-old man with a 10-year history of PD, with no previous history of psychiatric disorders, 2 months after the implant gradually developed manic symptoms and an increase of sexual interest, which gradually subsided 6 months later. Finally, 2 men affected by young-onset PD developed remarkable manic symptoms and changes in sexual behavior, which began a few days after the implant and lasted for some months, gradually disappearing spontaneously.

The latter 2 cases, described in some detail here, met the diagnostic criteria for manic episode.⁹

Patients and Methods

Quadripolar leads were implanted bilaterally in the STN under stereotactic guidance as described previously.² Stimulation was applied 24 hours a day. The patients were formally assessed 1 week, and 1, 3, 6, and 12 months after the implant in their best *on* state and in the practically defined *off* condition¹⁰

Transient Mania with Hypersexuality After Surgery for High-Frequency Stimulation of the Subthalamic Nucleus in Parkinson's Disease

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with the Unified PD Rating Scale (UPDRS) motor score.¹¹ Activities of daily living (ADL) were assessed by the ADL score of the UPDRS and the Schwab and England scale. The total levodopa-equivalent daily dose (LEDD) was calculated.² After the implant, antiparkinsonian medication was reduced to the lowest possible dose and stimulation was increased progressively. On each follow-up assessment, the stimulation settings were adjusted until the best overall clinical response was obtained. Behavioral and neuropsychological evaluations were carried out in all the patients treated with STN HFS, preoperatively and 3, 6, and 12 months after the implant, according to the after procedure. Cognitive assessment was carried out using a neuropsychological test battery¹²; the patients remained in the *on* period during cognitive assessment. Mood and anxiety were evaluated by means of Zung's self-rating scales for depression and anxiety¹³; the patients received structured psychiatric interviews to detect behavioral or psychiatric problems. Historical or ongoing psychiatric disorders were classified according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.⁹

Patient 1

A 52-year-old, right-handed man presented with an 11-year history of severe rigid-akinetic PD with moderate resting tremor that responded poorly to medication (levodopa [L-dopa] 400 mg/day, pergolide 5 mg/day). Before surgery, in the *off* state, UPDRS motor score was 60, and ADL score was 31.

There was a personal and family history of psychiatric disorders. At age 26 years, the patient suffered from a major depressive episode during his father's terminal illness. One of his sisters also presented an episode of major depression in her youth, which was treated successfully with antidepressants.

The patient received a bilateral STN implant in July 1999. Postoperative imaging confirmed that contact 1 of the right lead was in the right STN, while contact 0 of the left lead was in the left STN. Immediately after electrode placement and in the absence of STN stimulation, there was a dramatic improvement in the parkinsonian motor symptoms that lasted for about 7 days, probably due to transient functional inactivation of STN. Three days after the implant, preliminary STN stimulation was started. Compared to preoperative assessment, UPDRS motor score were improved by 67%, 55%, and 83%, respectively at 3, 6, and 12 months, while ADL score improved by 71%, 87%, and 86.8%, respectively (Table 1). Wearing-off phenomena and *on*-state dyskinesias disappeared. All antiparkinsonian medica-

tion was discontinued 1 month after surgery. Stimulation settings remained unchanged from the second month on (Table 1). Neuropsychological testing during follow-up showed no significant changes compared to preoperative performance. No noticeable change was detected in neuropsychological tests assessing attention, as compared to preoperative performance.

Two days after the implant (1 day before the initiation of STN stimulation) the patient developed a manic syndrome, characterized by inflated self-esteem and grandiosity, marked increase in goal-directed activities. This led to purchase of unneeded items, decreased need for sleep, planning of hazardous business investments, and flights of ideas. In addition, sexual desire, sexual fantasies, and sexual activity increased. These changes interfered significantly with the patient's social life and relationships.

Despite a lack of aptitude for, or interest in, religion, he began to spend much of his time writing poems on religious themes. He also became prodigal, purchasing books of every sort, and planned to open an artistic workshop or a tourist centre in the south of Italy. He began driving his car in a reckless manner, or as he himself described it "at the rhythm of rock and roll." Although he was not on dopamine agonists, he had frequent spontaneous erections and his sexual desire increased "like when I was twenty." At the same time, mood lability and quarrelsomeness developed, and he became irritable, litigious, and over-reactive. His appetite decreased and he lost 5 to 6 kg. Although his mood was steadily elevated, he also showed increased empathy for the suffering of others and a tendency to cry. Positive psychotic symptoms, such as hallucinations, delusions, catatonia, and conceptual disorganization did not occur. He could turn the generator on and off using a magnetic switch. When he turned off stimulation, which he did for less than 1 hour because of resurgence of motor impairment, there was a marked worsening of parkinsonian motor symptoms, but the manic symptoms did not resolve. Changes in the stimulation settings immediately affected motor abilities, but did not have any obvious effect on mood or behavior.

A diagnosis of manic episode was made. In agreement with the spouse, the patient was followed up very carefully and no pharmacological treatment for manic symptoms was prescribed. Three months later, the manic symptoms began to subside and eventually disappeared completely. Twelve months after the implant, the patient showed some reduction of initiative but no notable impairment in everyday life.

TABLE 1. Levodopa equivalent daily dose, energy delivered and clinical evaluations observed in 2 patients

	Before implant	1 week	1 mo	3 mo	6 mo	12 mo
Patient 1						
Levodopa-equivalent daily dose (mg)	900	760	0	0	0	0
Energy delivered (Watt $\times 10^{-6}$)	—	0.69	1.56	1.65	1.65	1.65
UPDRS motor score	60	22	20	20	27	10
UPDRS ADL score	31	—	2	9	4	4
Patient 2						
Levodopa-equivalent daily dosage (mg)	1800	1000	400	400	0	0
Energy delivered (Watt $\times 10^{-6}$)	—	0.30	0.86	1.94	1.92	2.16
UPDRS motor score	61	—	16	16	18	15
UPDRS ADL score	37	—	4	4	3	4

UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living.

Patient 2

This 42-year-old man had a 15-year history of severe PD, with resting and postural tremor and marked rigidity that could not be controlled adequately by drug treatment (L-dopa, 1,200 mg/day; pergolide, 6 mg/day). Before surgery, in the practically defined *off* state, UPDRS motor score was 61, and ADL score was 37 (Table 1).

In March 1999 he received a bilateral STN implant. Postoperative imaging confirmed that contact 0 of the right lead was in the right STN and contact 1 of the left lead was in the left STN. Immediately after electrode placement and in the absence of stimulation there was a remarkable improvement of motor symptoms, which lasted for 9 days. Two days after the implant intermittent STN stimulation was started. The voltage was increased gradually over a period of 3 months (Table 1). Motor symptoms greatly improved under stimulation; in particular, wearing-off phenomena, *off*- and *on*-state dyskinesias disappeared. Compared to baseline, at 3, 6, and 12 months UPDRS motor score respectively improved by 74%, 70%, and 75%, and ADL score by 89%, 92%, and 89% (Table 1). L-Dopa was reduced to 400 mg daily one week after the operation and all antiparkinsonian medication was stopped four months later. Neuropsychological testing during follow-up showed no postoperative changes in cognitive functioning. No noticeable change was detected in neuropsychological tests assessing attention, as compared to preoperative performance.

The patient had no personal or family history of psychiatric disorders except for alcohol abuse in his father. A tendency to cry and to be moved by trivial events, without mood changes, was noted some years before the implant.

The patient's manic symptoms started to develop 3 days after implant and few hours after the first STN stimulation session. He developed inflated self-esteem, labile mood and irritability, marked increase in goal-directed activities, increased sexual desire and sexual fantasies, and non-customary sexual behavior (inappropriate seductive behavior toward female medical staff and indiscriminate sexual encounters). His life changed markedly and, for the first time in several years, he resumed work and went on a journey with his wife. He wrote the manuscript for a short book about his experience with PD, started using a computer, and resumed his university course in astrophysics, which he had abandoned 15 years previously. His mood disturbance was associated with marked impairment of social relationships, as reported by his wife. He had no psychotic signs. A manic episode was diagnosed, but no medication was prescribed. The patient was carefully followed up with the cooperation of his wife.

When stimulation was discontinued, the parkinsonian motor symptoms worsened strikingly, but no changes in mania could be detected. The patient could not stand being without stimulation for more than few hours. When the stimulation settings were changed, motor signs were immediately affected, but the manic state persisted and no acute behavioral changes were observed. Six months after implant the mania started to abate and by 8 months there were no residual manic symptoms.

Discussion

The mood disorders observed in these 2 patients fulfilled the diagnostic criteria for a manic episode.⁹ In both cases, the episode started soon after the observation of motor improve-

ment after the implant, lasted for some months, and disappeared gradually. Both have been followed up for a total of 12 months, during which time there has been no recurrence of the symptoms. In both patients, mania was associated with remarkable motor improvement and resolved spontaneously, while the motor improvement persisted. The patients have not received any specific psychiatric treatment, which has allowed to observe the natural course of mood changes after STN implant. Attention did not appear to be affected by mania in these patients. The 3-month postoperative neuropsychological assessment of Patient 1, who showed the most severe manic symptoms, was carried out when the manic symptoms began to subside. In Patient 2, the manic symptoms began to subside 6 months after the implant; the 3-month postoperative assessment showed no change even on neuropsychological tests assessing attention, as compared to preoperative performance.

To our knowledge, this is the first report of a manic disorder in PD patients after the surgical procedure of bilateral STN HFS. Surgery is immediately suspected of being involved in inducing manic symptoms in these cases. Either the procedure, or the stimulation, or both, may have played a role in the appearance of manic symptoms. It is remarkable, however, that, although the motor condition had a strict time relationship with STN stimulation, this could not be demonstrated with manic symptoms. Reduction or discontinuation of STN stimulation for a matter of minutes caused immediate worsening of the motor condition, but did not influence behavior. Thus, the surgical procedure of lead implantation may have induced a reversible dysfunction of some neural cortical-subcortical circuits involved in mood, which could not be corrected by reducing stimulation for a short while. There was no morphological evidence of frontal damage on postoperative MRI scans, and the surgical procedure was identical to that of other patients who had no mood disturbance. The patients received dopaminergic treatment until the day before surgery; this was gradually reduced afterwards. In Patient 1, complete withdrawal was attained by the first month after implant, whereas in Patient 2 this occurred 4 months after the implant. It is remarkable, that in Patient 2 the manic symptoms lasted longer than in Patient 1.

Dopaminergic treatment before the surgical implant was well-tolerated by both patients in the present series. It is possible that the effects of STN implants added up to those of dopaminergic treatment, thus causing mood changes. In keeping with this, it has been demonstrated that STN HFS and dopaminergic treatment produce similar motor effects.² A synergy between dopaminergic treatment and HFS of the globus pallidum has also been observed in a patient who suffered from recurrent manic episodes shortly after the implant.¹⁴ Other factors that may be related plausibly to the development of manic symptoms include the exact point of electrode placement, the anatomical variations in the STN region⁶ and individual predisposition, such as a history of a mood disorder.

These clinical observations on PD patients receiving STN HFS provide an intriguing glimpse of the neural circuits possibly involved in depressive and manic disorders. We wonder whether cases were observed with a poor surgical outcome, in whom mania or psychotic depression occurred. Such observation could support a specific role of the surgical procedure or of other anatomical structures in generating mood changes, thus answering to some of the questions that are posed here.

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Steele-Richardson-Olszewski Syndrome in a Patient with a Single C212Y Mutation in the Parkin Protein

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Abstract: Steele-Richardson-Olszewski syndrome (SROS) is a neurodegenerative disorder of unknown aetiology, most frequently sporadic. Familial cases of SROS have been described. An intronic polymorphism of the tau gene is associated with sporadic SROS and mutations of the tau gene are present in atypical cases of SROS. The role of tau has been excluded in other families with pathology proven SROS, suggesting that this syndrome may have multiple causes. An 82-year-old patient, father of 3 children with autosomal recessive juvenile parkinsonism due to combined heterozygous mutations of the parkin gene, developed clinical features of SROS 2 years before death. The diagnosis was confirmed by pathology. He carried the C212Y mutation of the parkin gene and was homozygous for the A0 polymorphism and for the H1 haplotype. The role of parkin in the processing of tau is discussed. © 2002 Movement Disorder Society

Key words: Steele-Richardson-Olszewski syndrome; tau gene; parkin; PARK2

Steele-Richardson-Olszewski syndrome (SROS) was initially described as a combination of clinical findings characterized by akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and fronto-limbic dementia, and pathological abnormalities including neuronal loss, gliosis and presence of neurofibrillary tangles and neuropil threads, mainly in basal ganglia, diencephalon, brainstem, and frontal and temporal lobes.¹ SROS was soon renamed as progressive supranuclear palsy (PSP) and many investigators began to consider PSP as a new neurodegenerative disease.

The cause of SROS or PSP is unknown but toxic and infectious etiologies have been considered, based upon the pathological similarities with post-encephalitic Parkinsonism, metal poisoning and with the Parkinson–dementia complex of Guam.^{2–7} Because of the coexistence of cerebrovascular disease in some cases a vascular mechanism was also postulated.^{8–9} Atypical cases with characteristic pathological findings, but an incomplete clinical syndromes, have been described previously.¹⁰

Until recently PSP was considered a sporadic disorder, despite a small number of reports suggesting familial clustering.^{11–19} The gene responsible for the familial cases is unknown. Mutations of the tau gene were excluded in the majority of the families with familial PSP^{19,20} but there are some reports describing PSP-like syndromes in patients, occasionally members of families with typical frontotemporal dementia, with mutations of the tau gene.^{21–23} In addition, in sporadic

A videotape accompanies this article.

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