

Brief Reports

Inter-Rater Reliability of the International Cooperative Ataxia Rating Scale (ICARS)

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Abstract: We assessed the inter-rater reliability of the 100-point International Cooperative Ataxia Rating Scale (ICARS). Three neurologists independently rated videotaped ICARS examinations of 22 subjects with genetically determined ataxias (spinocerebellar ataxia [SCA] Type 1 in 11; SCA Type 2 in 1; Friedreich's ataxia in 10) and 4 controls. Scores on live ICARS assessment had ranged from 0 to 7 for controls and 11 to 74 for ataxic subjects (clinically very mildly affected to wheelchair-bound). Inter-rater correlation was very high for the total score (Kendall's ω 0.994, 95% confidence interval, 0.988–0.997), and high to very high for each component subscore (0.791 for speech to 0.994 for posture/gait). All correlations were significant at $P < 0.00001$. The ICARS exhibits very high inter-rater reliability even without prior observer standardisation and is sensitive to a range of ataxia severities from very mild to severe. © 2003 Movement Disorder Society

Key words: International Cooperative Ataxia Rating Scale; spinocerebellar ataxias; Friedreich's ataxia; reliability

Clinical rating of global ataxia severity is typically subjective. Although validated laboratory measures exist for some components such as stance,¹ eye movements,² and various aspects of limb function such as finger tap-

ping³ or single or multiple joint movements,^{4,5} most are too complicated for routine clinical use. The International Cooperative Ataxia Rating Scale (ICARS) was introduced in 1997 to provide a standardised clinical rating system for ataxia treatment trials.⁶ It has since been used for this purpose by several groups^{7–9} and has also been used to assess cerebellar signs in multiple system atrophy,¹⁰ although its inter-rater reliability has not been reported.

The semiquantitative 100-point ICARS itself consists of 19 items divided into four unequally weighted subscores: posture and gait disturbances (7 items; 34 points), (limb) kinetic functions (7 items; 52 points), speech disorders (2 items; 8 points), and oculomotor disorders (3 items; 6 points).⁶ The scale defines and semiquantitatively scores many of the classic clinical signs of the ataxic syndrome and, therefore, has high face validity for neurologists. The internal consistency (Cronbach's α) of the ICARS items is very high (0.93) in multiple system atrophy.¹⁰ Factor analysis of the 19 items confirmed a 4-factor solution corresponding to the subscale scores, with the exceptions that Archimedes spiral drawing (one of the seven kinetic function subscale items) did not load strongly on any factor and that nystagmus did not load strongly with saccadic pursuit and saccadic dysmetria on the oculomotor disorders subscale.¹⁰ As part of an ongoing study into the cognitive consequences of inherited ataxias, we videotaped ICARS assessments and determined inter-rater reliability.

SUBJECTS AND METHODS

A total of 11 subjects with spinocerebellar ataxia (SCA) Type 1 (confirmed genetically in at least 1 pedigree member), 1 with genetically confirmed SCA 2, 10 with genetically confirmed Friedreich's ataxia, and 4 spouse/partner controls (total = 26) underwent live videotaped ICARS assessment by a neurologist not specifically trained in movement disorders (E.S.). The videotapes were viewed and rated independently by 2 movement disorder specialists from other institutions (A.H., A.C.). These 2 raters did not have knowledge of the subjects' disease status. The original assessing neurologist also reviewed the videotapes and rescored the ICARS from them without recourse to the previous "live" scores, at an interval between 2 and 10 months after the "live" assessment. There was no prior discussion of the scale or training in its use by any of the 3 raters: each worked directly from the original publication.

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Nonparametric average measure intraclass correlations (Kendall's ω) for the three independent ratings of the global score and each subscale score from the videotaped ICARS assessments were calculated using SPSS software. The "live" assessment and the videotaped assessment performed by the original examining neurologist were also correlated as a measure of intra-rater and "live" versus videotaped examination reliability.

RESULTS

Subject ages were 37.6 years (average for ataxic subjects; range, 21–58 years) and 37.5 years (average for the 4 controls; range, 21–53 years). The range of ICARS scores on the "live" assessment of ataxic subjects was 11 to 74, correlating with clinical global impressions of very mildly affected to severely ataxic (wheelchair-bound).

The range of ICARS scores in the 4 control subjects was 0 to 7. The inter-rater and intra-rater ("live" vs. videotaped) average measure correlations and 95% confidence intervals are shown in Table 1. The correlations were highly significant ($P < 0.00001$) in all cases.

DISCUSSION

Our results show that the videotaped ICARS and its component subscales have good to excellent inter-rater reliability over a wide range of ataxia severities, even without standardisation. For comparison, the United Parkinson's Disease Rating Scale total motor score is reported to have a Kendall's ω correlation of 0.82,¹¹ considerably lower than the 0.994 reported here.

The posture/gait and the (limb) kinetic subscales showed the highest reliability. Despite this, the scoring instructions for the kinetic subscales are potentially confusing. For example, upper limb dysmetria/dyssynergia is rated at 1 for "oscillating movement without decomposition," and upper limb intention tremor rated at 1 for "simple swerve of the

movement." Rewording of these descriptors may improve clarity of separation of these abnormalities. The correlation was less strong (although still high) for the oculomotor and speech subscales. The oculomotor examination rates gaze-evoked nystagmus, saccadic (broken-up) pursuit, and saccadic dysmetria. Subtle degrees of each proved difficult to record unambiguously on videotape, which may explain some of the inter-rater variance. Speech was recorded clearly, and the variance probably relates to the inherent difficulty of describing degrees of dysarthria accurately and succinctly in print. A standard teaching tape would probably increase the reliability of this subscale.

The use of subjects with defined genetically determined ataxias in this study is advantageous in that it allows a confident diagnosis of ataxia to be made in those with very mild signs, about whom some doubt would otherwise exist. These very mildly affected subjects were still separated from controls on the total ICARS score, demonstrating that no appreciable ceiling effect exists. Similarly, the scale did not demonstrate a floor effect even for severely affected (wheelchair-bound) subjects. The linearity of the scale with disease progression remains to be established, however.

The use of subjects with such progressive ataxic syndromes precludes test-retest reliability assessment over a long enough period to obviate potential practice effects in the subjects or memory of individual subject's item scores in the tester. Nevertheless some reassurance as to intra-rater rating stability and as to the comparability of "live" versus videotaped assessments was provided by comparison of "live" and delayed videotaped assessments by the original examining neurologist. The tight total score correlation argues against unacceptable variability due to either of these factors. Ideally, however, the test-retest reliability of the ICARS should be established for subjects with relatively stable or very slowly progressive ataxic syndromes.

In conclusion, the ICARS and its component subscales have good to very good inter-rater reliability without standardisation, although a teaching tape would probably reduce variability of scoring for the speech subscale. The ICARS appears sensitive to the full clinical course of the progressive ataxias, although its linearity remains to be established. It may be videotaped as a satisfactory substitute for "live" assessment.

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TABLE 1. Inter-rater correlations for videotaped ICARS total and subscale scores, and intra-rater "live" vs. videotaped correlation

Rater/scale	Kendall's ω	Range (95% CI's)
Videotaped assessments (rated by 3 neurologists)		
Total ICARS score	0.994	0.988–0.997
Posture/gait subscale	0.994	0.989–0.997
Kinetic subscale	0.981	0.962–0.991
Speech subscale	0.791	0.598–0.899
Oculomotor subscale	0.990	0.987–0.998
"Live" vs. videotaped (neurologist, E.S.)		
Total ICARS score	0.990	0.987–0.998

ICARS, International Cooperative Ataxia Rating Scale; CI, confidence interval.

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Normal Dopaminergic and Serotonergic Metabolites in Cerebrospinal Fluid and Blood of Restless Legs Syndrome Patients

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Abstract: Cerebrospinal fluid (CSF) and blood obtained from 22 untreated or scarcely treated patients with moderate to severe restless legs syndrome (RLS; mean age, 58.6 ± 13 years) and 11 control subjects (mean age, 56.6 ± 12.9

years) were investigated for biogenic amines between 6:00 and 8:00 PM. We did not find any significant differences in the CSF concentrations of homovanillic acid, 3-orthomethyl-dopa, levodopa, 5-hydroxytryptophan, 5-hydroxyindoleacetic acid, tetrahydrobiopterin, dihydrobiopterin, 5-methyltetrahydrofolate, and neopterin. In addition, serotonin in whole blood and plasma activity of aromatic amino acid decarboxylase were all normal. Our results suggest that dopaminergic and serotonergic release is not substantially affected in RLS. © 2004 Movement Disorder Society

Key words: restless legs syndrome; pathophysiology; cerebrospinal fluid; dopamine; serotonin

The origin of restless legs syndrome (RLS) is unknown. Due to the excellent response of RLS symptoms to levodopa and dopamine agonists and the exacerbation of symptoms induced by dopamine antagonists,¹ abnormalities in the metabolism of dopamine in the nervous system could be expected to play a key role in its pathophysiology. However, positron emission tomography and single photon emission computed tomography studies, imaging presynaptic dopamine transporter or postsynaptic dopamine receptor binding capacities, reveal controversial results and overall no obvious dopaminergic deficit in RLS.^{2,3} Because serotonin reuptake inhibitors such as fluoxetine⁴ and sertraline⁵ aggravate RLS, involvement of the serotonergic system is also possible. A recent study of 16 RLS patients with a positive response to L-dopa or dopamine agonists (off dopaminergic or opiate medications) has shown normal morning CSF homovanillic acid (HVA), dihydrobiopterin (BH₂), and neopterin, slightly increased tetrahydrobiopterin (BH₄), and decreased 5-hydroxyindoleacetic acid (HIAA) levels.⁶ In this study, we investigated key metabolites of biogenic amine metabolism (Fig. 1), including CSF dopaminergic, serotonergic, and biopterin metabolites as well as whole blood levels of serotonin and the plasma activity of aromatic amino acid decarboxylase (AADC) in the early evening when symptoms of RLS are usually present.

PATIENTS AND METHODS

Twenty-two patients (17 women, 5 men; mean age, 58.6 ± 13 years; range, 26–81 years) with moderate to severe idiopathic RLS for 14.1 ± 13.1 years (range, 1–40 years) were included. Twelve patients suffered from early onset RLS (EO-RLS), which is characterised by a symptom onset before age 45, slow progression, and high familial aggregation. Ten patients had late-onset RLS (LO-RLS), a phenotype that starts after age 45, is usually rapidly progressive, and has limited familial aggregation.⁷ Ten patients had a positive family history (EO-RLS, n = 7; LO-RLS, n = 3). All patients met the

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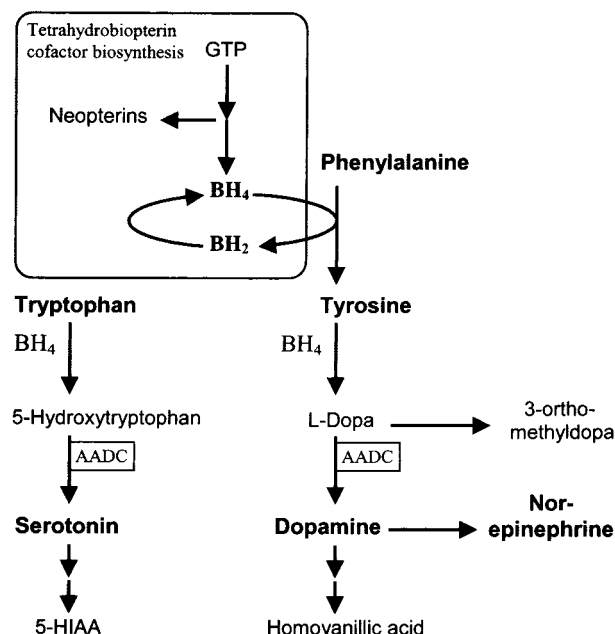


FIG. 1. Key metabolites in the metabolism of biogenic amines. GTP, guanosine triphosphate; BH₄, tetrahydrobiopterin; BH₂, dihydrobiopterin; AADC, aromatic amino acid decarboxylase; 5-HIAA, 5-hydroxyindoleacetic acid.

standardized diagnostic criteria of the International Restless Legs Syndrome Study Group,⁸ and neurological examination revealed no evidence of additional neurological or psychiatric disease. Before the study, a one-night polysomnography was performed in all patients who had lumbar puncture to further determine the severity of RLS. Seventeen patients had never been treated for RLS. Five patients had been treated previously with small dosages of levodopa but were taken off this medication at least 1 week before the study (Table 1). Controls consisted of 11 subjects (7 women and 4 men; mean age, 57.9 ± 14.0 years; range, 36–80 years) in whom RLS was clinically excluded and who were taking no psychotropic medication. Controls suffered from Bell's palsy (n = 4), transient ischemia (n = 4), motor neuron disease (n = 2), or radiculopathy (n = 1) and were comparable in age and body height.

Lumbar CSF and blood samples were collected between 6:00 and 8:00 PM in the prone patient using a standardized protocol. All parameters were analysed in the same portion and volume of CSF, and immediately frozen at -70°. Lumbar CSF was available in 18 patients, blood in all 22 patients. We determined the CSF concentrations of HVA, 3-ortho-methyl-dopa (3-OMD), L-dopa, 5-hydroxytryptophan (5-HTP), 5-HIAA, BH₄, BH₂, and neopterin, as well as 5-methyltetrahydrofolate (5-MTHF), a key metabolite in cytosolic methyl group

transfer. Serotonin concentrations were determined in whole blood and AADC activity in plasma. All metabolites were analysed by high performance liquid chromatography and electrochemical detection, as described previously.⁹ Experiments were performed in accordance with the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was given by all participants. Differences between patients and control subjects were analyzed by means of the Mann-Whitney *U* test. For correlation analysis, Spearman rank correlation coefficients were calculated. Results are reported as mean ± standard deviation. The significance level was set at $\alpha = 5\%$ with adjustment for multiple testing by the Bonferroni method.

RESULTS

CSF HVA did not significantly differ between RLS patients (208.0 ± 85.7 nmol/L) and controls (242.5 ± 109.5; *P* = 0.547). In addition, other dopaminergic metabolites such as CSF 3-OMD (31.0 ± 42.9 vs. 17.3 ± 8.2 nmol/L; *P* = 0.458) and L-dopa (4.0 ± 1.4 vs. 4.3 ± 1.3 nmol/L; *P* = 0.683) showed no abnormalities. The CSF serotonergic metabolites 5-HTP (5.8 ± 2.9 vs. 7.7 ± 4.1 nmol/L; *P* = 0.272), 5-HIAA (139.0 ± 66.6 vs. 134.9 ± 53.5 nmol/L; *P* = 1.000), and serotonin in whole blood (342.4 ± 174.1 vs. 368.2 ± 293.6 nmol/L; *P* = 0.950) were also within the control ranges. The CSF 5-HIAA/HVA ratio did not differ between patients (1.6 ± 0.6) and controls (1.8 ± 0.6; *P* = 0.458). Pterin metabolism also failed to reveal any abnormalities with normal CSF concentrations of BH₄ (21.7 ± 10.7 vs. 27.15 ± 13.4 nmol/L; *p* = 0.294), BH₂ (11.6 ± 9.6 vs. 7.6 ± 4.5 nmol/L; *p* = 0.577), and neopterin (21.4 ± 8.7 vs. 24.9 ± 6.7 nmol/L; *P* = 0.121). CSF 5-MTHF (56.7 ± 19.9 vs. 41.6 ± 18.2 nmol/L; *P* = 0.039) as well as the activity of plasma AADC (32.9 ± 10.6 pmol/ml/min vs. 37.7 ± 13.4 pmol/ml/min; *P* = 0.517) did not significantly differ between RLS patients and control subjects (Table 2). Furthermore, there were no differences between EO-RLS and LO-RLS in any of the analysed parameters and no significant correlation with the severity of RLS as measured by the International RLS Severity Scale or any sleep parameter (data not shown).

DISCUSSION

Our data confirm and extend the findings of Earley and colleagues.⁶ They recently reported normal HVA, BH₂, and neopterin, slightly increased BH₄, and decreased 5-HIAA concentrations in early morning (9:30 to 10:30 AM) CSF.⁶ However, differences in the BH₄ and 5-HIAA levels became evident only after age adjustment and were of unclear clinical significance. Because sensory

TABLE 1. Patient demographics

Patient no.	Age (yr)/ gender	Duration of RLS (yr)	Early onset	Family history	Previous RLS therapy	RLS severity (IRLS sum score)	SL (min)	TST (min)	SE %	PLM index	PLMS arousal index
1	54/m	4	No	Positive	100 mg L-dopa	23	5.0	320.0	67.0	16.4	6.9
2	48/f	2	No	Negative	No	25	68.5	367.5	75.1	6.3	3.8
3	56/m	15	Yes	Positive	No	26	290.5	159.5	33.0	93.5	48.9
4	81/m	5	No	Negative	No	25	0	0	0	82.7	0
5	73/f	40	Yes	Negative	100 mg L-dopa	29	165.0	252.0	53.0	32.7	10.2
6	62/f	40	Yes	Positive	No	31	80.5	315.0	74.0	66.4	47.8
7	26/f	15	Yes	Negative	No	19	14.0	453.5	93.0	5.1	0
8	47/f	10	Yes	Positive	50 mg L-dopa	29	11.5	375.5	85.0	8.3	4.5
9	47/f	2	No	Positive	No	22	58.0	344.5	71.0	22.4	7.0
10	80/f	25	No	Negative	No	20	21.0	281.0	59.0	23.9	33.0
11	66/f	1	No	Negative	50 mg L-dopa	-	134.0	226.5	48.0	110.4	44.5
12	49/f	2	No	Negative	No	29	34.0	374.5	82.0	66.5	66.8
13	56/f	20	Yes	Negative	No	30	130.5	248.0	52.0	58.2	5.6
14	62/m	7	No	Negative	No	31	70.5	277.5	52.0	63.4	74.2
15	55/f	38	Yes	Positive	No	33	25.5	355.0	77.0	32.6	30.4
16	39/f	5	Yes	Negative	200 mg L-dopa	26	38.0	274.5	57.0	59.1	60.1
17	72/f	3	No	Positive	No	29	53.5	284.0	58.0	83.0	84.5
18	64/f	7	No	Negative	No	-	15.0	339.0	69.0	4.7	2.1
19 ^a	60/f	25	Yes	Positive	No	18	-	-	-	-	-
20 ^a	55/f	10	Yes	Positive	No	26	210.0	138.5	28.0	161.1	114.4
21 ^a	66/m	5	No	Negative	No	24	-	-	-	-	-
22 ^a	70/f	30	Yes	Positive	No	35	52.0	223.0	47.0	57.0	6.7
						26.5	77.8	280.5	59	52.7	32.6

Mean of all patients.

^aSerotonin in whole blood analysis only.

SL, sleep latency; TST, total sleep time; SE, sleep efficiency; PLM index, periodic leg movements per hour time in bed; PLMS arousal index, PLMS associated arousal per hour total sleep time; f, female; m, male; —, not performed; IRLS, International Restless Legs Syndrome Study Group Severity Scale.

and motor symptoms of RLS are worse in the evening or night and peak in the hours immediately after midnight with a resolution in the late-morning hours (10:00 to 11:00 AM), it seemed possible that CSF studies performed in the morning would fail to pick up any underlying pathophysiological state in bioaminergic pathways in RLS. Due to the circadian rhythm of RLS, symptomatology pathophysiological studies are preferentially performed in the late evening hours,

ideally around midnight. Of course, it is rarely possible to carry out extensive studies during the night. We were able to study the patients in the early evening hours but failed to find any abnormalities. Because our patients suffered already from advanced RLS, it is also unlikely that the degree of severity of the disease accounts for the negative results. In addition, there was no significant correlation between any of the measured parameter and the subjective severity of

TABLE 2. Concentrations of dopaminergic and serotonergic metabolites in idiopathic RLS patients and control subjects

	RLS patients	Controls	P
CSF HVA (nmol/L)	208.0 ± 85.7	242.5 ± 109.5	0.547
CSF 3-OMD (nmol/L)	31.0 ± 42.9	17.3 ± 8.2	0.458
CSF L-DOPA (nmol/L)	4.0 ± 1.4	4.3 ± 1.3	0.683
CSF 5-HTP (nmol/L)	5.8 ± 2.9	7.7 ± 4.1	0.272
CSF 5-HIAA (nmol/L)	139.0 ± 66.6	134.9 ± 53.5	1.000
Serotonin (nmol/l, full blood)	342.4 ± 174.1	368.2 ± 293.6	0.950
CSF 5-HIAA/HVA	1.6 ± 0.6	1.8 ± 0.6	0.458
AADC activity (pmol/ml/min; plasma)	32.9 ± 10.6	37.7 ± 13.4	0.517
CSF BH4 (nmol/L)	21.7 ± 10.7	27.15	0.294
CSF BH2 (nmol/L)	11.6 ± 9.6	7.6 ± 4.5	0.577
CSF neopterin (nmol/L)	21.4 ± 9.6	24.9 ± 6.7	0.121
CSF 5-MTHF (nmol/L)	56.7 ± 19.9	41.6 ± 18.2	0.039

RLS, restless legs syndrome.

RLS as rated by the International RLS Severity Scale (IRLS) or objective polysomnographic parameters.

Besides RLS, Parkinson's disease (PD) is another disorder with an unequivocal symptomatic response to dopaminergic treatment. In contrast to RLS, a central biochemical dopamine deficit in the nigrostriatal system is well established in PD. Clinical symptoms are considered to appear when dopamine levels in the striatum have decreased by 50%. Although CSF monoamine measures may not reflect central events in detail, there is general agreement in the literature about a decrease in the levels of HVA, the principal metabolite of dopamine (which is reduced due to degeneration of dopamine-containing neurons) in lumbar CSF of PD patients.¹⁰ Normal CSF HVA values have been reported only in single parkinsonian patients with mild symptoms.^{11,12} In dementia, altered central nervous system (CNS) biogenic amines have also been demonstrated in single studies. In contrast to one study that showed normal CSF HVA and 5-HIAA in AD or senile dementia of the Alzheimer type (DAT),¹³ another study showed decreased HVA in DAT patients.¹⁴ Another study that compared DAT patients with and without extrapyramidal signs revealed significantly decreased CSF HVA and bipterins in those with extrapyramidal signs.¹⁵ In vascular dementia, CSF 5-HIAA and HVA concentrations are also significantly decreased.^{13,16} In major depression, CSF 5-HIAA¹⁷⁻¹⁹ and HVA^{18,19} have been shown to be normal.

The combination of the results obtained in this study and of those reported by Earley and coworkers suggest that parameters contributing to the dopaminergic and serotonergic release in RLS are either not altered or not sufficiently altered to be consistently detected in CSF. The positive and negative response of RLS symptoms to various drugs that act on different receptors in the CNS also makes it likely that these substances have a modulating effect and are not specifically or primarily involved in the pathophysiology of the disease; for example, beneficial drugs such as dopaminergics, opioids, benzodiazepines, or clonidine act primarily on dopamine, opioid, γ -aminobutyric acid, and α_2 -receptors, respectively. This hypothesis is supported by the finding that gabapentin, which does not exhibit affinity for many common receptor sites and does not alter the cellular uptake of dopamine, noradrenaline, or serotonin, has been shown recently to be effective in RLS.²⁰ In summary, our data support the hypothesis that the central dopaminergic and serotonergic release is not or is scarcely altered in RLS.

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Improvement of Sleep Quality in Patients With Advanced Parkinson's Disease Treated With Deep Brain Stimulation of the Subthalamic Nucleus

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Abstract: Most Parkinson's patients complain about sleep problems. The subjective effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on nocturnal disabilities and sleep quality was elucidated by the recently established Parkinson's disease sleep scale (PDSS). The DBS-treated group obtained significant improvement of motor function assessed by the Unified Parkinson's Disease Rating Scale. The mean total PDSS improved significantly after surgery whereas no change was found for the control group. Significant improvements of individual questions were obtained for overall sleep quality and motor symptoms whereas nocturia and daytime sleepiness did not change despite significant reduction of parkinsonian medication. © 2004 Movement Disorder Society

Key words: deep brain stimulation; subthalamic nucleus; Parkinson's disease sleep scale

Impairment of sleep is a major problem in Parkinson's disease (PD); nocturnal disabilities are reported by 96% of patients.¹ Both abnormal changes in central sleep regulatory centres and night-time symptoms, as described below, may contribute.^{1–4}

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Until recently, no formal scale existed to describe the different nocturnal disabilities that can impair sleep in PD. These have now been formalised into the Parkinson's disease sleep scale (PDSS) by Chaudhuri and colleagues,^{3,4} classifying symptoms as insomnia (sleep fragmentation, difficulty of sleep onset and maintenance), motor symptoms (restless legs, muscle cramps, dystonia), urinary (nocturia and incontinence) and neuropsychiatric symptoms (hallucinations, nightmares, and vivid dreams). In the preliminary evaluation, 115 patients (mean disease duration, 7.6 years), responded to the patient PDSS questionnaire. Nocturia was the most frequent symptom affecting sleep, followed by low overall sleep quality, daytime sleepiness, and motor symptoms. The patient response to the PDSS may be used to devise treatment strategies for nocturnal disabilities, including motor symptoms, in PD.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) has proven to be a valuable treatment for motor symptoms and complications in advanced PD.⁵ Improvement of tremor, rigidity, and bradykinesia allows reduction of levodopa (L-dopa) treatment, which is thought to be an important factor for the concomitant significant amelioration of dyskinesias.

In two different polysomnographic (PSG) studies of 11 insomniac patients with PD, DBS of the STN significantly increased sleep time, mainly by reduction of night-time motor symptoms, whereas periodic limb movements and motor behaviour during REM sleep was not alleviated in either study.^{6,7}

The purpose of this study was to evaluate patient response to the effect of STN-DBS on nocturnal disabilities assessed by the PDSS in patients with advanced PD compared with a control group of patients waiting for STN surgery.

PATIENTS AND METHODS

Study Subjects

Quality of sleep was studied in 2 groups of PD patients who completed the PDSS questionnaire. The surgery group consisted of 10 consecutive nondemented patients with advanced PD and motor complications who underwent operation between February and June 2002 (5 men and 5 women; mean age, 60.1 years; age range, 52–71 years; mean disease duration, 17.7 years; range, 10–28 years). Clinical status was evaluated for all patients before and after the operation by Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor score) and Hoehn and Yahr stage, and parkinsonian medication was registered.^{5,8} A control group consisted of 10 patients with advanced PD and motor complications admitted to

the waiting list for surgery (7 men, 3 women; mean age, 58.5 years; age range, 41–69; mean disease duration, 13.2 years; range, 5–20).

Instruments

Three different outcome measures were used. The PDSS^{3,4} is a visual analogue scale addressing 15 commonly reported symptoms associated with sleep disturbance. The PDSS is available in four languages, but had to be translated into Danish by the authors. The severity of symptoms is reported by marking a cross along a 10-cm line (labelled from worst to best state). Quantification is made by measuring the location of the cross on each line to the nearest 0.1 cm. Scores for each question ranges from 0 (symptoms severe or always experienced) to 10 (free of symptoms). Thus the maximum PDSS score is 150. The UPDRS is the clinical assessment of PD used most commonly; UPDRS part III was used to evaluate motor symptoms.

Surgical Procedures

Surgical procedures were carried out by a single neurosurgeon using the same method during the study period. Ten patients with advanced PD and medically intractable motor complications were treated with stereotactic and bilateral implantation of leads into the STN in a single operation. The patient was scanned with magnetic resonance immediately before the operation with the stereotactic frame (Leksell G frame; Elekta, Stockholm, Sweden) attached to the cranium, and coordinates for correct lead placement in the STN were calculated by means of a computer program (*Surgiplan v. 2.0*; Elekta). An electrical test stimulation was carried out during operation while the patient was examined by a neurologist for parkinsonian symptoms and adverse effects. With the leads (DBS lead 3389; Medtronic, Minneapolis, MN) in place, control magnetic resonance imaging (MRI) was carried out and on the same day, the leads were connected to a pulse generator placed subcutaneously in the subclavicular area. Programming of the pulse generator was started 2 days later.⁹

Data Collection

PDSS data were collected at two different times; information about the study and the questionnaire were mailed to the patients. Data for the surgery group were collected 1 month before surgery and 3 months after surgery, with a corresponding 4-month interval for the non-surgery group. Thus PDSS data were collected with an interval of 4 months in both groups. UPDRS and Hoehn and Yahr stage on and off medication was measured 2 to 4 weeks before and 3 months after the oper-

ation. Patients were evaluated in the hospital with the UPDRS part III in the morning after 12 hours of medicine fasting and again 1 to 1.5 hours later, after the usual morning dose of parkinsonian medication. In addition to the 15 PDSS questions, patients were asked whether they took any kind of sleep medicine.

Data were analysed by the *t* test for paired samples before and after surgery and for controls at baseline and 4 months later.

RESULTS

PDSS Scores

All STN surgery patients and patients on waiting list for surgery filled out the PDSS questionnaire. Mean total PDSS score (sum of question 1–15) before surgery was 79.8 and did not differ significantly from controls at baseline (mean total PDSS score, 87.4; $P < 0.515$). Total PDSS score increased significantly after surgery to 105.3 ($P < 0.022$). There was no significant difference between controls at baseline and 4 months later (87.4 vs. 85.8, respectively; $P < 0.732$). After surgery, total PDSS score of 105.3 differed significantly from the non-surgery group score of 85.8 ($P < 0.025$).

Mean score for each question increased significantly in 6 of 15 questions after surgery (Fig. 1). These included questions 1,2,4,11,12,13 addressing overall quality of sleep, difficulty in falling asleep, restless legs or arms, painful muscle cramps, painful posturing of arms or legs in the morning, and tremor on waking. In the control group, none of the questions differed significantly from baseline in the 4-month evaluation. As seen in Figure 1, there was a tendency for improvement in all questions except 8 and 9 concerning nocturia and incontinence at night, which may be caused by a nocturnal hyperactive bladder unrelated to motor problems and 14 and 15 concerning morning and daytime sleepiness.

UPDRS Score, Hoehn and Yahr Stage, Stimulation Parameters and Medication

Postoperative UPDRS rating was not completed for 2 of 10 patients, 1 patient did not want to stop with anti-parkinsonian medication overnight, and 1 patient was not available for follow-up. Before surgery, the mean UPDRS score off medication was 48.8, decreasing to 21.9 after surgery ($P < 0.002$) and Hoehn and Yahr stage off medication was reduced from 4.2 before surgery to 2.6 after surgery. The range of stimulation parameters for the surgery group was 2.6 to 3.5 V, 60 μ sec and 150 to 185 Hz. Medication in L-dopa equivalents including L-dopa and dopa agonist treatment was reduced by 29% from 1,138 to 813 mg. In the surgery group, benzodiaz-

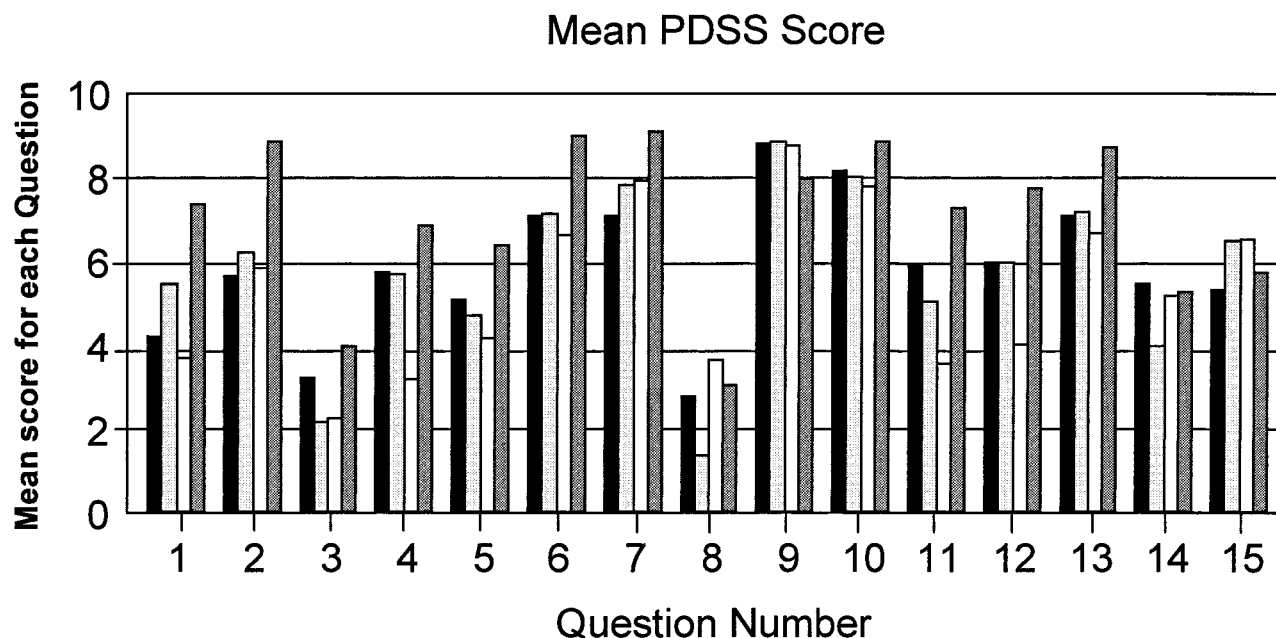


FIG. 1. The mean score for each of the 15 questions of the PDSS. A score of 10 signifies best state and of 0 worst state. Significant improvement of STN-DBS was found for question 1 ($P < 0.003$), 2 ($P < 0.010$), 4 ($P < 0.015$), 11 ($P < 0.009$), 12 ($P < 0.015$) and 13 ($P < 0.011$). No improvement was observed for questions 8, 9, 14 or 15.

Black bars: Series 1, control baseline. Light gray bars: Series 2, control 4 months later. White bars: Series 3, before surgery. Dark gray bars: Series 4, after surgery.

epines were used by 4 patients before and 2 after the operation. In addition, 2 used clozapine before and 1 after the operation. In summary, 5 patients before and 8 after surgery did not use sleep medicine or clozapine. In the non-surgery group, the corresponding figures were 7 patients at baseline and 8 patients after 4 months. In the surgery group, 2 patients used antidepressants before but not after surgery and 1 patient received treatment with a selective serotonin reuptake inhibitor after but not before surgery.

DISCUSSION

Patients with advanced PD treated with STN-DBS showed significant reduction in UPDRS part III and significant reduction in medical treatment as reported in a previous study of another group of patients from our institution.⁹ The mean total PDSS score improved significantly 3 months after surgery compared with mean total PDSS score 1 month before surgery.

In the control group matched for age and duration of disease, the mean total PDSS score remained unchanged during an interval of 4 months. The subjective PDSS was established by an English-German group to assess nocturnal symptoms contributing to sleep disturbances in individual PD patients.³ In the study by the English-German group the mean total PDSS score in patients

with advanced disease was 86 (lower than that of patients with early/moderate disease, which was 103) and did not differ much from the present score of the group planned to receive surgery (79.8) or from the present scores of the control group with an interval of 4 months (87.4 vs. 85.8).⁴

After surgery, the mean score for each question showed either significant improvement or a tendency toward improvement, except for scores for questions 8 and 9, concerning nocturia, and 14 and 15, concerning daytime sleepiness. The main effects of STN-DBS on individual PDSS scores were significant improvement of nocturnal motor symptoms and overall sleep quality. Improvement in overall sleep quality may be secondary to the reduction in motor symptoms by continuous STN stimulation day and night. Although a direct effect on surrounding structures involved in sleep regulation cannot be ruled out, it is not very likely with a stimulation range of 1-2 mm from the central part of STN. Our findings are supported by two other studies of the effect of STN-DBS on sleep quality.^{6,7} In these two studies, PSG recordings were carried out for 11 insomniac PD patients treated successfully with STN stimulation.^{6,7} In the first study, recordings were made in two all-night sessions, one with and one without stimulation.⁶ STN-

DBS reduced night-time motor symptoms and improved total sleep time, although periodic leg movements and REM sleep behaviour disorders did not improve. It was concluded that insomnia in PD patients may result from night-time motor disability.⁶ In the second study, PSG recordings were carried out before and after surgery, subjective evaluation of sleep was assessed by the Pittsburgh sleep quality index (PSQI), and daytime sleepiness was estimated by the Epworth sleepiness scale.⁷ Seven of eight patients showed significant improvement of the PSQI questionnaire after surgery and PSG recordings showed an increase in the longest period of uninterrupted sleep.⁷

In the present study, nocturia was a serious symptom before surgery. After surgery with improvement of motor symptoms and overall sleep quality, nocturia was reported to be the most serious nocturnal symptom, in agreement with results described previously Chaudhuri and associates.³ In this study, nocturnal hyperactive bladder symptoms did not seem to improve with STN stimulation.¹⁰

No change was reported for daytime sleepiness, which otherwise might have been expected due to significant improvement in overall sleep quality and significant (29%) reduction in antiparkinson medication. Difficulty staying asleep or sleep fragmentation improved but remained a main problem after surgery. Thus, daytime sleepiness may have explanations other than reduced sleep quality and medical treatment. It may be related to PD pathology, perhaps abnormalities in central sleep regulatory centres and inappropriate REM sleep onset during the daytime.^{2,11} In a recent study of PD and sleepiness, severity of sleepiness was not dependent on nocturnal sleep abnormalities, motor and cognitive impairment, or antiparkinsonian treatment.¹²

In conclusion, the results of the subjective response to the PDSS suggest improvement of sleep quality by STN-DBS primarily due to a significant reduction of night-time motor symptoms, whereas nocturia, sleep fragmentation, and daytime sleepiness seem unaffected. It is therefore suggested STN-DBS does not ameliorate bladder dysfunction and possible disturbances of central sleep regulatory centres. These results should be explored further with a larger series of patients and controls.

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TABLE 1. Questions of the Parkinson's disease sleep scale

Question no.	Question
1	The overall quality of your night's sleep.
2	Do you have difficulty falling asleep each night?
3	Do you have difficulty staying asleep?
4	Do you have restlessness of legs or arms at night or in the evening causing disruption of sleep?
5	Do you fidget in bed?
6	Do you suffer from distressing dreams at night?
7	Do you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?
8	Do you get up at night to pass urine?
9	Do you have incontinence of urine because you are unable to move due to "off" symptoms?
10	Do you experience numbness or tingling of your arms or legs which wake you from sleep at night?
11	Do you have painful muscle cramps in your arms or legs whilst sleeping at night?
12	Do you wake early in the morning with painful posturing of arms or legs?
13	On waking do you experience tremor?
14	Do you feel tired and sleepy after waking in the morning?
15	Have you unexpectedly fallen asleep during the day?

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Phenotypic Characterization of DYT13 Primary Torsion Dystonia

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Abstract: We describe the phenotype of DYT13 primary torsion dystonia (PTD) in a family first examined in 1994. A complete neurological evaluation was performed on all available family members: 8 individuals were definitely affected by dystonia. The family was re-evaluated in March 2000: at that time, 3 more individuals had developed symptoms of dystonia. Inheritance of PTD was autosomal dominant, with affected individuals spanning three consecutive generations and male-to-male transmission. Age at onset ranged from 5 to 43 years. Onset occurred either in the craniocervical region or in upper limbs. Progression was mild, and the disease course was benign in most affected individuals; generalization occurred only in 2 cases. We did not find anticipation of age at onset or of disease severity through generations. Most subjects presented with jerky, myoclonic-like dystonic movements of the neck or shoulders. DYT13-PTD is an autosomal dominant disease, with incomplete penetrance (58%). Clinical presentation and age at onset were more variable than in DYT1-PTD, and the neck was involved in most of those affected. Moreover, the individuals with generalised dystonia were not severely disabled and were able to lead independent lives. To date, this is the only family with DYT13-PTD. © 2004 Movement Disorder Society

Key words: primary torsion dystonia; PTD; DYT13; family study; phenotype

Dystonia is a syndrome characterised by sustained involuntary muscle contractions, causing twisting and repetitive movements or abnormal postures.^{1,2} The current classification includes two major etiologic categories: primary (sporadic or familial) and symptomatic dystonia. Primary torsion dystonia (PTD) is a movement disorder in which dystonia is the sole abnormality attrib-

utable to the condition, in the absence of other neurological signs and without any known cause.³ The precise prevalence of familial cases is unknown; on the basis of the largest series of patients affected by dystonia, it accounts for less than 20%.⁴ Familial dystonia is a clinical and genetic heterogeneous entity with a wide range of phenotypic expressions; to date, one gene and several different loci have been linked to different presentations of PTD.

In 1994, we studied a large Italian family, with several members affected by PTD (Fig. 1). The phenotypic presentation of dystonia among the affected individuals was variable, the prevalent phenotype consisting in early onset, upper body segmental dystonia. This family underwent genetic analysis; linkage with the DYT1 locus on chromosome 9q34 was ruled out⁵; successively, the linkage with DYT6 and DYT7 was also excluded.⁶

Due to the large number of affected individuals, the family was considered suitable for a genome-wide search. This strategy allowed mapping a novel locus, DYT13, on chromosome 1p36, to a 22 cM region with high gene density.⁷ Until now, the linkage with the DYT13 region has been detected only in the family described. The phenotype of DYT13-PTD has not yet been reported in detail, so we present here a description of the clinical presentation of dystonia in the definitely affected members.

SUBJECTS AND METHODS

The family was studied for the first time in 1994. All family members were investigated for possible causes of secondary dystonia using a detailed questionnaire and received a complete on-site neurological examination.⁵ Each subject was videotaped during the assessment, and a senior neurologist viewed the videotapes. Examination included tasks designed to reveal minor signs of dystonia, or of other movement disorders. The final diagnosis (affected, not affected, or probably affected) was established with the agreement of all the examiners.

All family members were re-evaluated in March 2000, using the same methodology described above. During the last visit, the disability of the affected individuals was also assessed by means of a section of the dystonia rating scale designed to assess the residual function in daily routine tasks (speech, writing, eating, swallowing, hygiene, dressing, and walking). The score ranged from 0 to 4 (0–6 for walking).⁸ The family genotype was analysed by excluding linkage with DYT1⁵, DYT6, and DYT7 loci in affected individuals.⁶ A genome-wide search allowed mapping a novel locus (DYT13) on chromosome 1p36.⁷

A videotape accompanies this article.

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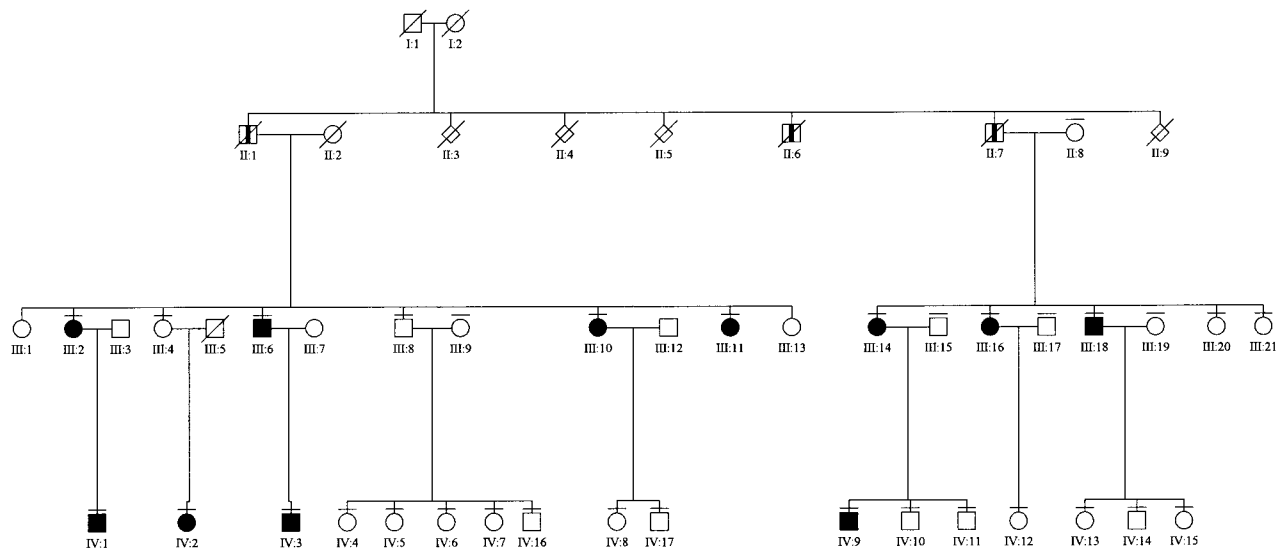


FIG. 1. Simplified pedigree of the family. Black symbols denote individuals affected by primary torsion dystonia, a thick vertical bar within the symbol denotes individuals affected by history. Deceased members are marked by a diagonal line. A thin horizontal bar above a symbol indicates members who were examined clinically.

RESULTS

Family Data and Clinical Features

This family included 45 members and 11 spouses. Ancestors and all family members originated from a small region on the pre-Apennine highlands. In 1994, we identified 8 definitely affected subjects (III:2; III:6; III:10; III:14; III:16; III:18; IV:1, and IV:3). All available individuals were re-evaluated approximately 6 years later (March 2000). At that time, 3 more individuals (III:11, III:20, and IV:9) had developed symptoms of dystonia. Two of them were unaffected in 1994; the third presented with mild symptoms, which at that time did not allow to diagnose a definite dystonia. The remaining 5 individuals, diagnosed as probably affected in 1994,⁵ did not present appreciable progression over 6 years. They still had minor clinical signs (jerks of the neck or of the arm or mild tremor), but no spasmodic movements or abnormal posture were evident, no abnormal directional or task-induced movements, and no sensory tricks. In conclusion, after the last visit in March 2000, 11 members were diagnosed as affected by dystonia. The history and clinical presentation in individuals with a definite diagnosis of dystonia is described below in some detail and is summarised in Table 1. The scores of the disability scale are analytically reported in Table 2.

Affected Subjects

III:6.

A 67-year-old man is the index case. His personal history was uneventful until the age of 10, when cervical and head trauma were caused by a 6-metre fall (the patient reported the head trauma as “severe,” although he was not hospitalised). At the age of 15, he presented with abnormal movements of the head, described as rapid (clonic) rotational movements and lateral head tilt. The clinical picture was stable until the age of 46. After a high fever (over 42°C), cervical dystonia worsened without spreading to other body regions. Several years later, he developed right arm dystonia, which started with task-induced dystonic movement and rapidly progressed to dystonia at rest. Drug treatment did not produce clinical improvement. At age 54, he underwent surgical resection of the right sternocleidomastoid muscle without clinical benefit. During the first evaluation in 1994 (see Video, Segment 1), he had segmental dystonia, involving the cranial–cervical segment and the right upper limb. Symptoms consisted in involuntary jerks of the head and of the right shoulder, inducing a tremulous right rotational torticollis, pain and rigidity of the neck, and hyperlordosis. The patient had abnormal posture of the right wrist and dystonic movements of both arms (more severe on the right side). Because of upper limb dystonia, the patient was clumsy in performing tasks such as writing, drawing, or handling objects.

TABLE 1. *Clinical presentation and progression of dystonia in the affected subjects*

Subject	Age at onset (yr)	Presentation at onset	Age at last visit (yr)	Progression event-related	Presentation at last visit	Distribution at last visit	Disability (Overall score, Burke et al., 1985 ⁸)	Response to therapy
III:2	5	Cranial–cervical	71	No	Cranial–cervical Upper limbs	Segmental	Severe (10)	No
III:6	15	Cervical	67	Yes. High fever	Cranial–cervical Upper limbs	Segmental	Mild (4)	No (L-dopa 200×4) Neuroleptics Artane
III:10	26	Cervical	63	Yes. After first pregnancy	Cranial–cervical upper limbs	Segmental	Moderate (6)	
III:11	?	Cervical	65	No	Cervical	Focal	Mild (0)	
III:14	5	Upper limbs	61	Yes. After first pregnancy	Cranial–cervical Limbs, trunk	Generalised	Moderate (7)	
III:16	5	Cervical	59	No	Cranial–cervical Trunk	Segmental	Mild (2)	No (L-dopa 200×4)
III:18	20	Cervical	56	No	Cranial–cervical Limbs	Generalised	Moderate (6)	
III:20	?	Cervical	53	No	Cranial–cervical	Segmental	Mild (1)	
IV:1	43	Right upper limb	45	No	Right upper limb	Focal	Mild (1)	
IV:3	14	Cranial–cervical	32	No	Cranial–cervical	Segmental	Mild (4)	
IV:9	?	Upper limbs	41	No	Cranial–cervical Upper limbs	Segmental	Mild (1)	

III:2.

A 76-year-old woman suffered from fever-related seizures during infancy. Dystonic symptoms in the upper body (cranial–cervical and upper limbs) were noted since the age of 5. She had a head trauma and right arm fracture at age 18, without any consequence for the progression of dystonia. The patient and her relatives reported that she was fully symptomatic since the onset and that progression was noted only in terms of severity of symptoms. No spreading of dystonia to other body regions was observed. A pregnancy (ended in a caesarean delivery) and surgery for kidney stones did not

influence dystonia. Different combinations of oral drugs and botulinum toxin treatment did not substantially improve dystonia. During the last visit, the patient presented segmental dystonia: moderate cranial–cervical involvement, and severe upper limb dystonia, which disabled the use of both upper limbs (see Video, Segment 2). She was unable to write, and needed help in the tasks of daily life requiring fine hand and finger movements.

III:10.

A 68-year-old woman had an uneventful personal history until the age of 20, when she was cured with

TABLE 2. *Dystonia Disability Scale*

	Speech (0–4)	Handwriting (0–4)	Feeding (0–4)	Eating/swallowing (0–4)	Hygiene (0–4)	Dressing (0–4)	Walking (0–6)	Total (0–30)
III:2	1	3	2	0	2	2	0	10
III:6	0	1	1	0	1	1	0	4
III:10	1	1	1	1	1	1	0	6
III:11	0	0	0	0	0	0	0	0
III:14	1	2	1	0	1	1	1	7
III:16	0	1	0	0	0	0	1	2
III:18	1	2	1	0	1	1	0	6
III:20	0	1	0	0	0	0	0	1
IV:1	0	1	0	0	0	0	0	1
IV:3	1	1	1	1	0	0	0	4
IV:9	0	1	0	0	0	0	0	1
Average	0.45	1.27	0.63	0.18	0.54	0.54	0.18	3.82

Scale from Burke et al.⁸

penicillin for rheumatic fever. During childhood she stuttered. She had three pregnancies and a miscarriage. She reported the onset of jerky movements of the head when she was age 26, after the first pregnancy. Later, dystonia progressed to involve pharyngeal and laryngeal muscles; as a consequence, the patient had difficulties in swallowing and reported hypophonia and voice tremor.

During the last examination, she presented with segmental dystonia of the cranial and cervical muscles, larynx, and upper limbs (see Video, Segment 3). Dystonic movements of the neck consisted of backward jerks and gross irregular head tremor. She presented also tremor and dystonic posture of the hands but was able to write a trembling (but still understandable) calligraphy.

III:11.

A 65-year-old housekeeper had an uneventful medical history. She was unaware of any involuntary movement. When examined in 1995 at the age of 60, she presented slight involuntary tilt of the head and tremor of both hands during the finger-to-nose test, but no dystonic posture or movement was evident. When re-evaluated in 2000, she presented torticollis and left-hand dystonia and was diagnosed as being definitely affected by segmental dystonia. The symptoms did not impair daily life activities.

III:14.

A 61-year-old woman reported phobic symptoms starting in youth. She presented hand dystonia at the age of 6 and reported that, almost since the onset of the disease, she had a shaking tremor involving all the body. A mild occipital trauma was reported at age 7. She had 3 pregnancies; after the first one at the age of 26, she noted that the severity of dystonia had progressed. At the time of her last evaluation, she presented with dystonic dysphonia, dystonic posture of the head and upper limbs (more evident in the right arm), and shaking tremor of the head, trunk, and legs (see Video, Segment 4). Axial and limb dystonic tremor was more evident when she was seated and was enhanced when speaking. Upper limb dystonia moderately impaired feeding, writing, and handling small utensils, but the overall disability was mild (see Table 2), i.e., she could conduct domestic activities.

III:16.

A 59-year-old woman reported a nervous breakdown in her thirties. Several years ago, she was treated with increasing doses of levodopa (up to 200 mg q.i.d.) without any clinical improvement. She had two pregnancies (one ended in miscarriage), which are not reported to

have influenced her dystonia. At the moment of the evaluation, she presented with involuntary movements of the upper and lower face (more evident when speaking), painful dystonic posture of the neck (right laterocollis), dystonic posture of both arms, involuntary movements of the fingers (evident when walking), and writer's cramp. She also had marked scoliosis with hypertrophy of paravertebral muscles and hyperlordosis, with abnormal truncal posture when walking.

III:18.

A 56-year-old man reported the onset of a mild cervical dystonia at the age of 20. Dystonia did not progress over the following 3 decades; in his fifties he experienced a mild worsening of symptoms, consisting in dystonic posture of right hand and involuntary movements of both hands and head. At the time of evaluation, he presented with scoliosis, tremulous dysphonia, dystonic tremor of hands, and involuntary movements of the lips and eyes (see Video, Segment 5). The subject also reported early morning painful contractures of both legs and rapid jerky movements of the neck; this latter symptom sometimes woke him up at night. Dystonia moderately affected writing and other daily chores, but he could work as a farm laborer engaged in a full-time physical job.

III:20.

A 58-year-old woman was diagnosed as probably affected by cervical dystonia in 1994. When re-evaluated 6 years later, she was definitely affected and presented with dystonic posturing of the right arm while writing and dystonic jerks and posturing of the neck partially controlled by a sensory trick. Her writing was moderately clumsy and words were legible.

IV:1.

A 45-year-old employed man had an uneventful personal history until the age of 40, when he noticed that writing had become painful and distressing; this forced him to change the way he held the pen and modified his handwriting style. At the time of evaluation, he presented with writer's cramp, which did not excessively impair his handwriting. He also presented an abnormally high blink rate that he had noted since adolescence. In the 5 years after onset, symptoms of dystonia were reported as stable.

IV:3.

A 32-year-old man was delivered pre-term with forceps and experienced normal psychomotor developmental stages. At the age of 14, he stuttered and had tic-like

movements of facial muscles. During the first evaluation in 1994, he presented with rapid tic-like movements in left upper and lower facial muscles, frequent irregular blinking, mild dysphagia with occasional choking (when drinking), voice tremor, stuttering and hypophonia, dystonic movements of the neck, and scoliosis (see Video, Segment 6). During writing, he presented abnormal posturing of the hands and jerky myoclonic-like movements of the neck, that forced the head to extend backward. When re-evaluated, 6 years later, no progression of dystonia was observed.

IV:9.

This 41-year-old man was unaffected in 1994. When re-evaluated 6 years later, he presented with marked irregular tremor and bilateral dystonic posturing of upper limbs and writer's cramp. He is aware of a painful neck posturing of recent onset, but he is not aware of dystonia of the upper limb, which perhaps started a few years ago. During writing, he has some tic-like movement of the face.

DISCUSSION

This family affected by DYT13-PTD includes 11 affected subjects spanning three generations. The observation of the affected individuals during a 6-year interval (from 1994 until 2000) allowed us to depict the phenotype of DYT13-PTD in the family. Onset was variable in terms of age (ranging from 5 to over 43 years) but was homogeneous with regards to the presentation at onset. Dystonia invariably involved the upper body: the cranial-cervical region (in 8 patients; 73% of cases) or the upper limbs (in 3 patients; 27%). Progression was mild and the disease course relatively benign in all affected individuals. All the patients with long disease duration experienced a spread of symptoms to other body regions. Progression led in 7 cases (64%) to a segmental involvement, in 2 cases (18%) to generalization; in the remaining 2 other cases (18%) there was no progression and the disease remained focal. The time course of progression could not be established with accuracy because most patients were not completely aware of their symptoms. Crossed interviews of different family members allowed us to establish that progression was quite heterogeneous. Two subjects took notes of their disease progression, which clearly showed heterogeneity. In subject III:14, onset was during infancy, and symptoms since then consisted of tremor involving all the body and progressed almost imperceptibly into old age. Subject III:6 was affected by torticollis since age 15, but progression of dystonia only occurred after 30 years, with spread to the right shoulder and arm.

Such long delay between onset and the spread of symptoms is unusual among PTDs. There is consensus on the observation that most PTD cases, particularly those with early onset, progress within 5 years from onset.^{9,10} It is very uncommon that dystonia only progresses after decades. We reviewed the records of the PTD patients in the Gemelli Registry (Elia and colleagues, unpublished data). In a series of 360 sporadic PTD patients with a mean disease duration of 8.6 years (± 8.5), 40% had a progression of dystonia: in 65% of them symptom spread occurred during the first 5 years, whereas 35% reported over a longer period (in none did dystonia progress after 10 years).

In 3 subjects, the progression of dystonia was related to specific events: in 2 of 6 affected women, pregnancy was related in time with onset (III:10) or progression (III:14). One of the patients (III:6) experienced symptom exacerbation after an acute fever. It is worth noting that several patients reported relevant traumatic events: none was related to disease progression. No correlation between the severity of the disease and age at onset was seen, and no anticipation occurred between generations.

At the last visit, the disability score was low in all the affected family members (even those with onset in infancy), and this finding is surprising when one considers the long disease duration. Compared with DYT1-PTD, the individuals with generalized dystonia were not severely disabled: they could lead normal daily lives (see Table 2).

One gene and four PTD loci have been identified (see Table 3). The clinical picture in the DYT13-PTD is noticeably different from the DYT1 phenotype, where dystonia presents in a limb, rarely affects the cranial-cervical region, and has a higher tendency to generalize, producing a much more disabling disease.^{11,12} The DYT6-phenotype is characterized by a greater number of body regions involved at onset and in the course of the disease, which tends to be more severe and to generalize more frequently.¹³ The phenotype in our family is also different from that described in PTD linked to the DYT7 gene, which is characterized by adult-onset and pure focal cervical dystonia without tendency to spread to other body regions.¹⁴

In several PTD families reported in the literature, linkage to the known PTD loci has been excluded; in some of these families, the phenotype shares relevant clinical features with DYT13 dystonia, and we may argue that they carry the same gene defect of this family. In two large non-Jewish families reported in 1996 by Bressman and coworkers (one previously described by Uitti and Maraganore¹⁵), the affected members presented with early or adult-onset dystonia confined to cervical

TABLE 3. *Features of PTD linked to the known loci*

	DYT 13 (1p36)	DYT 1 (9q34)	DYT 6 (8p21–22)	DYT7 (18)
Age at onset	Variable (5–43)	Childhood–adolescence	Variable (Average: 18.9)	Adult (28–70)
Distribution of dystonia at onset	Cranial–cervical or upper limb	Limb (frequently lower)	Variable	Cervical
Prevalent phenotype	Segmental, upper body	Generalised, limb involvement, spared craniocervical	Segmental, upper body	Focal, craniocervical
Generalization	Infrequent	High (to other limbs and axial muscles, infrequent to cranial–cervical muscles)	High	No
Severity	Mild	Severe	Severe	Moderate
Progression	Slow	Rapid	Rapid	No
Transmission	AD	AD	AD	AD
Penetrance	58%	30–40%	30%	< 40%

PTD, primary torsion dystonia; AD, autosomal dominant.

and brachial regions.¹⁶ Two other PTD families, of Swedish and Italian origin, had a similar phenotype: variable age at onset (spanning from the second to the fifth decade), prominent cranial–cervical involvement, and upper limb tremor or occasional generalization.^{17,18} An Italian family from South Tyrol had an unusually variable phenotype: most affected members had cervical or upper limb dystonia with onset in adulthood, although some patients suffered from typical early onset generalized dystonia.¹⁹ Some of these families may link to the DYT13 locus, as many of them were characterized by variable age of onset (juvenile or adult) and prominent cranial–cervical involvement.

In summary, the prevalent phenotype of DYT13-PTD is an early onset segmental upper body dystonia with a benign course and frequent association of dystonic postures and slow movements with myoclonus-like jerks of neck and shoulders. The role of this new dystonia locus remains to be tested in other PTD families and in the general population, as it should be noted that most patients affected by cranial–cervical or upper limb (focal or segmental) dystonia have a sporadic occurrence, which may reflect the clinical expression of a gene with low penetrance such as the DYT13.

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Legends to the Video

Segment 1. Subject III:6, index case. The patient is sitting and talking; cervical dystonia, mild blepharospasm, mild breathing dysphonia, and right limb dystonia are evident. Neck dystonia is complex, with prevalent rotational right-oriented, antecollis and left head tilt. Sensory tricks (touching the nape with the left hand and pulling up and forward the shoulders) allow correction of head position for a very short time. The neck is asym-

metric, as the right sternocleidomastoid muscle had been resected. When walking, the rotational rapid jerks of the head and antecollis are accentuated. The abnormal posture of right upper limb is evident: the dystonic posture of the right wrist (flexed) and slow abnormal movements of the hand are visible. Writing causes myoclonic jerks backward of the neck and an irregular tremor of the head. Bilateral writer's cramp (more severe in the right hand) is illustrated.

Segment 2. Subject III:2, sister of the index case. The patient is sitting; cervical dystonia, moderate blepharospasm, mild breathing dysphonia, and upper limb dystonia (action-induced in the right limb; at rest in the left side) are evident. Dystonic posture and tremor of the neck are visible. Fine movements and finger taps of right upper limb are very clumsy as they induce dystonia in the hand and arm; she is unable to perform finger to nose test with her left hand. Performing tasks with both hands also induces abnormal orolingual movements. When walking, abnormal posture of the left upper limb is evident. Writing induces myoclonic jerks of the head. The patient cannot write with either hand.

Segment 3. Subject III:10, sister of the index case. The patient is sitting; neck is in a sustained posture of right laterocollis. When she turns her head right, she presents dystonic tremor of the neck. Speaking reveals tremulous voice and dysphonia. Writing induces jerks of the neck and pulls the head forward.

Segment 4. Subject III:14, cousin of the index case. Sitting: the patient has a severe tremor of all the body segments, most pronounced in the trunk, neck, and lower limbs. When the patient speaks, the dystonic tremor of the neck accentuates, and a rotational right-oriented torticollis becomes evident; the patient tries to use a *geste antagoniste* of the right hand to correct the position of the head. Fine movements of the upper limbs are clumsy. Tremor affects mostly upper body while legs are possi-

bly involved only with transmitted jerks when sitting, and the patient is able to walk, her gait being largely normal. During writing, the neck and shoulders are pulled backward by a massive myoclonus-like jerk.

Segment 5. Subject III:18, cousin of the index case. He presents with tremulous spasmodic dysphonia; while speaking, upper limbs dystonic tremor and involuntary movements of the lips and eyes (excessive blinking) are evident. When writing, he presents perioral dyskinesias and some jerky movements of neck and upper limbs.

Segment 6. Subject IV:3, son of the index case. When sitting, he presents with upper and lower face dystonia and excessive and prolonged blinking. When speaking, voice tremor and stuttering are evident and he presents with perioral dyskinesias as well as dystonic movements of the neck. Writing discloses myoclonic jerks of the neck and shoulder muscles.

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Parkinson's Disease Patients With Bilateral Subthalamic Deep Brain Stimulation Gain Weight

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Abstract: Weight, body mass index (BMI) and energy expenditure/energy intake (EE/EI) was studied in 19 Parkinson's disease (PD) patients after subthalamic deep brain stimulation (STN-DBS) versus 14 nonoperated ones. Operated patients had a significant weight gain (WG, + 9.7 ± 7 kg) and BMI increase (+ 4.7 kg/m²). The fat mass was higher after STN-DBS. Resting EE (REE; offdrug/ON stimulation) was significantly decreased in STN-DBS patients, while their daily energy expenditure (DEI) was not significantly different. A significant correlation was found among WG, BMI increase, and pre-operative levodopa-equivalent daily dose, their reduction after STN-DBS, and the differential REE related to stimulation and the REE in the offdrug/OFF stimulation condition. In conclusion, STN-DBS in PD induces a significant WG associated with a

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reduction in REE without DEI adjustment. © 2004 Movement Disorder Society

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Advanced stages of Parkinson's disease (PD) are characterized by motor fluctuations. Weight loss often occurs, probably due to increased energy expenditure (EE).¹⁻³ Whereas reduced total daily activity may reduce EE,⁴ it may be raised by motor fluctuations and severity of motor symptoms, particularly dyskinesias.² Bilateral subthalamic nucleus deep brain stimulation (STN-DBS) has proved effective both on parkinsonian symptoms and motor fluctuations.^{5,6} Recently, unexpected adverse events of STN-DBS were described such as behavioral and psychiatric disorders.⁵⁻⁷ Like other investigators,^{5,6,8-13} we had noticed that STN-DBS-treated PD patients gain weight. In an exploratory retrospective study,¹³ we assessed the weight and body mass index (BMI = kg/m²) of 22 consecutive PD patients who underwent bilateral STN-DBS. Most of them (83%) gained weight as early as 3 months after surgery, an effect that persisted for at least 1 year with a mean gain of 9.65 kg. Forty-two percent had a BMI $\geq$ 25 (overweight or obesity) at the last visit (mean follow-up = 18 months). In this retrospective chart review, we found that men, patients with the highest presurgery levodopa-equivalent daily dose (LEDD) and those with the highest motor scores in the *off* condition seemed more at risk of weight gain (WG). In a recent report, a positive correlation was also found between WG and reduction of drug-induced dyskinesias after surgery.⁷ These results suggest that STN-DBS modifies the energy expenditure/energy

intake (EE/EI) balance in relation to motor symptoms and drug intake changes. To test this hypothesis, we designed the present prospective study to analyze the morphometric and metabolic variables (EE/EI) in two groups of PD patients, one after STN-DBS surgery and one nonoperated group from the waiting list, and correlated changes with those of clinical variables. We also sought to determine whether the weight gain mainly involves the fat mass rather than the muscle mass.

PATIENTS AND METHODS

Patients

Thirty-three PD patients fulfilling the inclusion criteria for STN-DBS¹⁴ were included in the study. The patients gave their written informed consent to the protocol, which was approved by the local ethics committee review board (CCPPRB-Bordeaux-B). The NST-DBS group included 19 operated PD patients compared with 14 nonoperated patients from the surgery waiting list (No STN-DBS = control group). The patients characteristics are indicated in Table 1.

Surgery

Surgical procedures were performed by the same neurosurgeon. Quadripolar electrodes (Medtronic, DBS-3389 electrode, Minneapolis, MN) were implanted in both STN and connected to a subcutaneous programmable pulse generator (Itrel II or Kinetra, Medtronic) with a conventional procedure establishing the optimal functionally defined target referenced to a line drawn from the anterior commissure (AC) to the posterior commissure (PC; 12.33 $\pm$ 1.34 mm lateral to AC-PC line, 10.70 $\pm$ 1.26 mm anterior to PC and

TABLE 1. Patient characteristics

Characteristic	Nonoperated no STN-DBS n = 14	Operated (before) STN-DBS n = 19	Difference
Age (yr)	61.5 $\pm$ 10.9	59.9 $\pm$ 6.60	NS
Gender (M/F)	8/6	11/8	NS
Disease duration (yr)	12.2 $\pm$ 4.0	15 $\pm$ 3.2	NS
Hoehn and Yahr <i>off</i>	3.7 $\pm$ 1.0	4.2 $\pm$ 0.8	NS
UPDRS-III <i>off</i>	46 $\pm$ 16	55.2 $\pm$ 17	NS
Dyskinesia (AIMS- <i>on</i>)	5.4 $\pm$ 5.6	12.5 $\pm$ 12.6	NS
LEDD (mg/day)	1009 $\pm$ 260	993 $\pm$ 408	NS
MATTIS score	132.9 $\pm$ 6.8	135 $\pm$ 4.8	NS
Beck score	10.00 $\pm$ 8.0	08.22 $\pm$ 7.4	NS

Patient characteristics include demographic variables, parkinsonism severity (Hoehn and Yahr and UPDRS-III motor examination), dyskinesias as rated *on* during a levodopa challenge test by the Abnormal Involuntary Movement Scale (AIMS), levodopa-equivalent daily dose per day (LEDD mg/d), cognitive status (MATTIS), and depressive symptoms (Beck Depression Inventory).

UPDRS-III, Unified Parkinson's Disease Rating Scale-III; STN-DBS, subthalamic nucleus deep brain stimulation; NS, not significant.

$-2,70 \pm 1.92$ mm below AC–PC line).¹⁴ Continuous monopolar stimulation was used (130 Hz, 1.5–3 V, pulse width 90 μ sec).

Clinical Evaluation

Both patient groups were evaluated by the same standardized procedure during an acute levodopa challenge test (CAPIT)¹⁵ before surgery (control group) and before and after surgery (STN-DBS group). For subsequent analysis, the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) was divided into three subscores: tremor (items 20, 21), rigidity (item 22), and akinesia (items 23–26, 31). Dyskinesias were evaluated using the Abnormal Involuntary Movements (AIMS) -dyskinesia rating scale (12 items, maximum score = 48, graded 0–4).¹⁶ The Beck Depression Inventory¹⁷ was performed before and after surgery to evaluate mood changes and the MATTIS scale to evaluate cognitive changes. We also calculated LEDD, according to previously proposed conversion factors.¹⁰

Anthropometric Measures, Percentage of Body Fat, and Metabolic Evaluations

We collected data regarding weight and BMI (weight in kg/height² in m²), calculated body composition using two different methods, and analyzed resting energy expenditure in both groups. Anthropometric measures were performed by the same investigator according to the procedures described in the Anthropometric Standardization Reference Manual.¹⁸ This approach consisted of measuring the triceps, biceps, subscapular, and suprailiac skinfold thickness using a Harpenden compass. The sum of the four skinfold thicknesses determined a range of values convertible into percentage of fat mass using the Durnin and Womersley equation.¹⁸ Dual-energy X-ray absorptiometry (DEXA) measurements were made with a total body scanner (QDR 45000 apparatus; Expert, Lunar, France). DEXA measured the attenuation of X-rays pulsed between 70 and 140 kV. Known absorptive properties scanned alongside each subject made it possible to analyze attenuation changes and to determine tissue composition, including fat mass and percentage of body fat. Energy expenditure was estimated by resting EE (REE, cal/kg fat-free mass per minute) measured by indirect calorimetry (IC) using a Delatrac Metabolic Monitor (Datex, Helsinki, Finland).¹⁹ A transparent acrylic hood is placed over the subject's head and shoulders and expired air is sucked from the hood continually. Measurements of oxygen consumption and carbon dioxide production were performed to calculate REE, expressed per kilograms of fat free mass (FFM) to control for age variations. Daily energy expenditure (DEI) was

recorded using a dietary interview (covering 7 days) administered by a dietician.¹⁹

IC was performed in the morning in patients confined to bed after 12 hours fasting. For each experimental condition, measurements were noted after 30 minutes. The REE was obtained in the control group in the following experimental conditions: (1) *off* drug (at least 12 hours after the last ingestion of levodopa) = D-; and (2) *on* drug, 45 minutes after a levodopa challenge test (Madopar dispersible: 200 mg levodopa/50 mg benserazide, Roche France) = D+. In the STN-DBS group, four experimental REE conditions were obtained: the same (1) drug *off* = D- and (2) drug *on* drug = D+ conditions, as in the control group, but also with either the STN-DBS stimulation turned (3) OFF = S- or (4) ON = S+, in a random order, thus giving the following: stimulator *off*-drug off = S–D–, stimulator *off*-drug on = S–D+, stimulator *on*-drug off = S+D–, and stimulator *on*-drug on = “S+D+” experimental conditions and REE variables.

Statistical Analysis

Variables were compared with an unpaired or paired *t* test, a Mann–Whitney test, or a Wilcoxon signed rank test when appropriate. Correlations were made by Pearson or Spearman *r* correlation tests when appropriate. The level of significance was set at 5% alpha error.

RESULTS

Patient Characteristics

There was no statistical difference between the two groups in demographic variables, parkinsonism severity scores (Hoehn and Yahr and UPDRS-III motor examination), dyskinesias scores as rated *on* during a levodopa challenge test by the AIMS, LEDD per day, cognitive status (MATTIS), and depressive symptoms (Beck Depression Inventory) as indicated in Table 1. Apparent difference in AIMS scores was not significant due to large standard deviations and low numbers.

Motor Outcome of STN-DBS

All operated patients greatly improved on their UPDRS-III *off* drug motor score by approximately 60% ($P < 0.005$) as well as in the *on* drug condition ($P < 0.05$). Also, akinesia, tremor, rigidity, and AIMS subscores improved (Table 2).

Activity of daily living (Schwab and England) was significantly improved after STN-DBS ($P < 0.005$). It was possible to reduce the mean levodopa equivalent daily dose intake by 50% ($P < 0.005$).

Of the 19 STN-DBS-operated patients, 10 had some adverse events: infection of the pulse generator in 1,

requiring removing plus antibiotic treatment and reimplantation 3 months later without further complications, mild dysarthria–hypophonia ($n = 7$), moderate and intermittent euphoria in 1, some gait instability at long-term follow-up in 3.

Body Weight and Fat Mass Changes Induced by STN-DBS

The STN-DBS group had a mean weight (70.3 ± 14.8 kg) after surgery, which was not significantly different from that of the control group (65.8 ± 15.3 kg). In 1 patient, included in the metabolic study, the weight before surgery could not be accurately obtained; thus, the mean weight gain was calculated on 18 STN-DBS-operated patients. All patients after STN-DBS gained weight (mean $+ 9.7 \pm 7$ kg; $P < 0.0001$) at the mean postsurgery follow-up of 12.7 ± 7.8 months. Individual weight changes are indicated in Table 3. The mean WG tended to be higher in men than in women (respectively, $+12.2$ kg vs. $+ 6.2$ kg), but this difference did not reach statistical significance ($P = 0.11$). Similarly, BMI significantly increased in patients after STN-DBS (before surgery $= 20.6 \pm 3.5$ kg/m², after surgery 25.3 ± 4.3 kg/m²; $P < 0.0001$). A total of 3 patients (16%) became obese (BMI ≥ 30 kg/m²) and 7 (37%) had a significant WG (BMI ≥ 25 kg/m²; Table 4). Analysis of body composition performed by the anthropometric and DEXA methods in the two groups showed a percentage of fat mass higher in the PD patients after STN-DBS than before (controls), with a gain of approximately 3.5% (mean of results obtained with the two methods; Table 4).

Energy Expenditure and Metabolic Balance

Table 5 demonstrates that the REE for S+D– was significantly ($P < 0.05$) decreased in STN-DBS patients compared to: (1) The nonoperated group and (2) Within this operated group compared to the nonstimulated condition with or without levodopa = S–D– or S–D+, respectively. The DEI of STN-DBS stimulated patients, however, was not significantly different compared to control nonoperated patients. IC also showed that stimulation ON normalized the REE ($P < 0.001$). The levodopa challenge test had the same effect but to a lesser extent ($P < 0.05$). In the control group, there was no significant REE change after levodopa. However, it should be noted that 2 control patients had a very high REE (mean 39.75 FFM cal/kg per minute compared to 23.9 FFM cal/kg per minute for the other 12).

Correlations of Weight and Metabolic Changes With Clinical Variables

In the STN-DBS group, no correlation was found between WG or BMI increase and patient age, age at onset, disease duration, the MATTIS mean score, the BECK Depression Inventory mean score, which did not change after surgery. Moreover, mean Hoehn Yahr, mean UPDRS-III S–D+ motor score changes after STN-DBS, or each of its subscores (akinesia, rigidity, tremor) were not correlated with WG or with BMI increase. Dyskinesia scores improved in the S+D+ condition, but this correlated neither with WG nor with BMI increase.

A significant correlation was found between preoperative LEDD, LEDD reduction, and both WG ($r^2 = 0.5$,

TABLE 2. Scores and dose before and after surgery

STN-DBS group	Before surgery		After surgery			
	D–	D+	S–D–	S–D+	S+D–	S+D+
UPDRS-III	55.2 ± 17.8	16.9 ± 9.3	50.3 ± 13.6	$22.1 \pm 2.1^{a,b}$	$19.8 \pm 9.3^{a,b}$	11.4 ± 6.4
Akinesia score	20.5 ± 9.2	6.8 ± 5.5	20.1 ± 6.6	$8.8 \pm 9.4^{a,b}$	$8.9 \pm 6.6^{a,b}$	4.7 ± 5.3^a
Tremor score	9.6 ± 6.2	0.8 ± 0.9	8.8 ± 7.2	3.6 ± 7.1^a	2.2 ± 3.8^a	0.5 ± 1.1^a
Rigidity score	9.2 ± 4.3	3.8 ± 2.9	8.5 ± 4.7	$3.5 \pm 3.7^{a,b}$	2.4 ± 2.6^a	1.2 ± 1.2^a
Dyskinesia (AIMS)		2.5 ± 12.6		6.7 ± 8.2		6.63 ± 7.9
LEDD (mg/d)	993 ± 408				402 ± 351	
Beck score	8.22 ± 7.4				11.5 ± 8.4	
MATTIS score	135 ± 4.8				135 ± 6.9	

Motor scores and levodopa-equivalent daily dose (LEDD) before and after surgery in subthalamic nucleus deep brain stimulation (STN-DBS) group.

Lower case a indicates statistically significant difference ($P < 0.05$) in motor score between S–D– and S–D+ or S+D– or S+D+ conditions. Lower case b indicates statistically significant difference ($P < 0.05$) in motor score between S+D+ and S–D+ or S+D– conditions. Before surgery, each motor score was statistically different between D– and D+ conditions. P values calculated by Wilcoxon signed rank test.

S, stimulation; S+, stimulator turned on; S–, stimulator turned off; D, levodopa drug challenge; D+, on drug; D–, off drug; UPDRS-III, Unified Parkinson's Disease Rating Scale, motor section; AIMS, Abnormal Involuntary Movement Scale; Beck, Beck Depression Inventory.

TABLE 3. Individual weight changes after STN-DBS in patients who underwent the metabolic evaluation after surgery

Patient no.	Before STN-DBS (kg)	After STN-DBS (kg)	Weight gain (kg)
1	NA	89	NA
2	62	67	5
3	47	63	18
4	60	73	13
5	56	87	31
6	66	71	5
7	55	56	1
8	60	74	14
9	74	75	1
10	59	69	10
11	56	69	13
12	79	85	6
13	33	38	5
14	44	51	7
15	78	87	8
16	41	45	4
17	80	92	13
18	55	66	11
19	61	71	10

STN-DBS, subthalamic nucleus deep brain stimulation; NA, missing data.

$P < 0.05$; $r^2 = 0.46$, $P < 0.05$, respectively) and BMI increases ($r^2 = 0.5$, $P < 0.05$, both).

The differential REE induced by STN-DBS (ON minus OFF stimulation) and REE S–D– were correlated with WG ($r^2 = 0.4$, $P = 0.01$ and $r^2 = 0.5$, $P = 0.02$, respectively). The differential REE induced by STN-DBS was also strongly correlated with the mean UPDRS-III S–D– score ($r^2 = 0.8$; $P = 0.0005$).

No other correlation was found between REE and clinical variables (rigidity, akinesia, tremor, dyskinesia) or motor improvement (UPDRS-III and its subscores *off* drug-OFF stimulation minus *on* drug-ON stimulation), either globally or regarding each subscore. The mean LEDD score before and after STN-DBS and its reduction after STN-DBS were not correlated with REE.

DISCUSSION

The present study shows that WG occurs after NST-DBS in almost all stimulated PD patients. By using two validated methods, we further demonstrate that the WG is mostly a fat mass gain. Moreover, this weight change was due to decreased energy expenditure without any adjustment of energy intake.

It is conceivable that most of the patients “normalized” their weight compared to their premorbid status. However, this theory needs to be directly demonstrated by a prospective long-term study. Indeed, it is well known that, during the course of PD, almost half of the patients experience weight loss, which may be as much as 10 kg in approximately a quarter of all cases.^{20–22} This weight loss mainly involves the fat mass rather than the muscular mass.^{23,24}

However, this “normalization” hypothesis cannot fully account for the finding that 11% of our STN-DBS-treated patients became obese (BMI ≥ 30) and that 21% became pathologically overweight (BMI ≥ 25). This WG occurred as early as in the first 3 months and continued to increase slowly beyond 1 year,¹³ a finding also observed in the recent retrospective study by Gironell and colleagues.¹¹

To further explore this issue, we investigated risk factors for WG after STN-DBS. No correlation was found between age at onset, mean disease duration, and the age of patients and WG patients. Men were found to be more at risk in our retrospective pilot study,¹³ but this preliminary result could not be confirmed by the present study or by the results of Romito and associates (men = mean + 8.3 kg, women = mean + 9.8 kg).⁷ Of interest, the WG in the latter study was quite similar to what we found. The same was true in the recent retrospective study by Barichella and coworkers in which 29 of 30 patients had a mean WG of 9.3 kg (mostly during the first 3 months after surgery, as in our study). Moreover, there was no difference between men (8.9 kg) and women (10.3 kg). The WG persisted at 1 year follow-up, as in our study.¹² Approximately a fourth of their

TABLE 4. Metabolic evaluation in nonoperated PD group (control group) and in STN-DBS group before and after surgery

PD patient groups	Controls	STN-DBS before	STN-DBS after
Weight (kg)	65.8 $\pm$ 15.3	59.2 $\pm$ 13	70.3 $\pm$ 14.8 ^a
BMI (kg/m ²)	23.2 $\pm$ 2.9	20.6 $\pm$ 3.5	25.3 $\pm$ 4.3 ^a
Patients obese	7.7%	5%	16%
Patients overweight	23%	16%	37%
Percentage of fat mass (%)			
Anthropometric	23.8 $\pm$ 7.7		26.5 $\pm$ 7.6
DEXA	20.4 $\pm$ 8.4		24.9 $\pm$ 11.6

^a $P < 0.0001$ between STN-DBS before and after surgery calculated by paired *t* test.

BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; PD, Parkinson's disease; STN-DBS, subthalamic nucleus deep brain stimulation.

TABLE 5. DEI and REE in two groups of patients

PD patient groups Experimental conditions	DEI (kcal/day)	REE (FFM cal/kg per min)			
		S-D-	S-D+	S+D-	S+D+
Controls (n = 14)	2,396 ± 770	26.4 ± 3.1	27.1 ± 8.3 ^a	—	—
STN-DBS (n = 19)	2,253 ± 947	26.4 ± 8.4	22.7 ± 3.7 ^a	21.0 ± 2.3 ^{b,c}	20.7 ± 2.6 ^{b,c}

Daily energy intake (DEI) and resting energy expenditure (REE by fat-free mass, FFM) assessed by indirect calorimetry in 19 PD patients undergoing bilateral subthalamic nucleus deep brain stimulation (STN-DBS) and 14 patients awaiting operation. S, stimulation; D, levodopa drug challenge; +, on; −, off. Lower case “a” indicates statistical significance ($P < 0.05$) between two variables; lower case “b” indicates statistically significant ($P < 0.05$) difference in REE between S+ and S− conditions within STN-DBS group; lower case “c” indicates statistically significant ($P < 0.05$) difference in REE between stimulated conditions S+D− and S+D+ in STN-DBS group compared to conditions in No STN-DBS group.

P calculated by paired and unpaired *t* test.

patients were in the overweight range (in accordance with our results) and declared “they had never gained such weight during their entire lives.”

In our study, we did not find any strong correlation between WG and motor parameter changes, in contrast with the pallidotomy study by Ondo and colleagues that reported a positive correlation between tremor improvement and WG.²⁵ In the study by Gironell and associates, a positive correlation between UPDRS motor subscore (rigidity, akinesia, tremor) improvement with WG was observed in a PD group after DBS,¹¹ but the study used retrospective data and included both pallidal and STN-DBS. Further studies investigating the correlation between WG and motor parameter changes, thus, are mandatory, probably by studying more patients prospectively and using various semiquantitative or quantitative measures.

Previous metabolic studies in PD demonstrated that the REE increase usually ranges between 20 and 51% compared to control subjects.^{1–3} Only one study demonstrated a decrease in free-living EE due to reduced motor activity and possibly reduced energy intake.⁴ It has been proposed that rigidity was the most likely factor explaining increased REE.^{2,3} There is also some evidence that tremor might also increase EE.¹ For example, Louis and coworkers observed lower BMI in patients affected by essential tremor compared to controls and suggested that this phenomenon was due to an increased EE.²⁶ In our study, we observed a positive correlation between REE and UPDRS motor scores in the *off* condition but not with any of the UPDRS motor subscores chosen (akinesia, rigidity, tremor). The REE decrease was also correlated with UPDRS motor score improvement both after STN-DBS is turned on and the levodopa challenge test. Levodopa-induced dyskinesias is clearly another candidate to account for the REE increase in PD.²⁷ Improvement in dyskinesia might thus be a factor of reduced EE, EE/EI imbalance, and consequently of WG. This hypothesis follows from the results reported by Gironell and colleagues.¹¹ We could not demonstrate any clear correlation between the AIMS mean score and the mean

RE, but this determination, again, would require further analysis in a prospective study involving more patients and using complementary methods of analysis.

There is evidence from our study of an REE/DEI ratio imbalance in STN-DBS-operated patients. While their REE decreased, the DEI of the patients studied remained at the same level as in nonoperated patients. In this respect, DEI was cautiously studied through a completely standardized and validated dietary interview.¹⁹ This strategy is at odds with the recently published abstract of Barichella and colleagues, reporting that 52% of their 29 patients became hungrier and increased their food intake after STN-DBS.¹²

Why STN-DBS-stimulated PD patients do not adjust their DEI to their new REE status requires further investigation. A regional effect of STN-DBS on the satiety hypothalamic centers remains very hypothetical, because WG has been reported to occur in medial pallidotomy-treated patients and because increased DEI is rather uncertain.^{25–27} An alternative explanation is an effect more or less directly linked to dopaminergic drug dosage reduction after STN-DBS.²⁸ Hypothalamic dopaminergic transmission in PD is reduced with neuronal cell loss in the lateral hypothalamus, which is well known to be involved in food-intake regulation.^{29–31} Thus, dopaminergic stimulation or overstimulation might be involved in a new dopamine hypothalamic homeostasis in PD that further undergoes imbalance after drastic dosage reduction after STN-DBS. Dopamine is also well known to play a role in the mesolimbic circuit that modulates motivation and reward behaviors, perhaps including food intake.^{32,33} A recent study using PET C-11 raclopride (a D₂ dopamine receptor ligand) demonstrated that striatal dopamine D₂ receptor levels were significantly lower in obese patients than in controls.³² Moreover, mean BMI in this obese group was negatively correlated with mean D₂ receptor linkage parameters. In psychoses, it is also well known that neuroleptics, which block dopamine receptors, increase appetite and often lead to dramatic WG.³⁴ The positive correlation between WG and BMI

increase and levodopa-equivalent dose intake before STN-DBS on one hand and its further reduction after STN-DBS on the other hand strongly suggest that dopamine is involved in weight change in PD after STN-DBS.

In conclusion, STN-DBS is associated with WG, which may occur in the pathological range in a subgroup of patients. STN-DBS candidates should be fully informed of this possible side effect, and patients with STN-DBS-induced overweight should be suitably managed. Further prospective long-term studies are mandatory to confirm the present results and to further analyze the causes and consequences of STN-DBS-induced WG. We believe that changes in dopamine drug intake possibly along with reduced dyskinesia severity may play a central role in energy imbalance and consecutively in WG, but this theory needs further investigation.

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