Acute and chronic effects of anteromedial globus pallidus stimulation in Parkinson's disease

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Abstract

***Objective*—To evaluate the effects of acute and chronic stimulation in the anteromedial part of the globus pallidus internus (GPi) on the symptoms of patients with Parkinson's disease.**

***Methods*—Six patients with severe Parkinson's disease (Hoehn and Yahr stage 4–5 in "off" drug condition) with motor fluctuations and levodopa induced dyskinesia (LID) were operated on. Chronic electrodes were implanted in the anteromedial GPi bilaterally in five patients and unilaterally in one patient. The effect of stimulation via the four contacts for each electrode (n=11) was assessed postoperatively on the contralateral parkinsonian signs in the off condition and on the contralateral and ipsilateral LID in the "on" condition. The core assessement program for intracerebral transplantation protocol was performed before surgery and then 1, 3, and 6 months after surgery in on and off conditions and in on and off stimulation conditions.**

***Results*—Stimulation performed postoperatively showed a significant improvement ($p<0.05$) by 47% (contralateral rigidity) and 32% (contralateral bradykinesia) when stimulation was applied through the distal contact. Levodopa induced dyskinesias were improved by 95% (contralateral LID) and by 66% (ipsilateral LID) when stimulation was applied through the distal contact. Six months after the surgery, GPi stimulation in the off condition led to a mean improvement in the motor score of UPDRS by 36%. The mean daily duration in the off state decreased by 52% ($p<0.05$). The mean duration of LIDs decreased by 68% ($p<0.05$) and their severity by 53% ($p<0.05$).**

***Conclusion*—Chronic stimulation in the anteromedial GPi shows that this is a safe and effective treatment for advanced Parkinson's disease with benefit sustained for at least 6 months.**

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Keywords: Parkinson's disease, chronic stimulation, globus pallidus

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Motor complications, such as levodopa induced dyskinesias (LIDs) and motor fluctuations, commonly occur in patients with Parkinson's disease chronically treated with levodopa.[1] Changing the treatment such as spreading out levodopa doses throughout the day, using sustained release levodopa, and adding dopamine agonists usually temporarily improves motor complications, which can reappear and worsen when the disease progresses.

Surgical treatment may be proposed to patients not satisfactorily improved by medical treatment. Recently, there has been a resurgence of interest in pallidotomy for the treatment of advanced Parkinson's disease. This surgical procedure dramatically reduces contralateral LIDs but also improves all cardinal parkinsonian signs such as rest tremor, rigidity, bradykinesia, and gait dysfunction.[2–9] Equivalent results have recently been shown with chronic high frequency deep brain stimulation, which is an alternative surgical nonlesional treatment for Parkinson's disease.[10–13]

Currently, the optimal lesion site of pallidotomy or pallidal stimulation remains uncertain.[14] In the early 1950s neurosurgeons investigated lesion of the anterodorsal region in the internal portion of the globus pallidus (Gpi).[15 16] In 1960, Svennilson *et al*[17] reported that stereotactic lesions in the ventroposterolateral pallidum markedly improved the clinical results. Since the recent surgical reassessment of pallidotomy by Laitinen *et al*,[2] neurosurgeons have performed pallidotomy or high frequency deep brain stimulation in the ventroposterior GPi. However, a recent report has shown a dramatic improvement of cardinal parkinsonian signs in a patient after bilateral chronic anterior pallidal stimulation.[10]

In an attempt to confirm the results of this pilot study and thus to re-evaluate the anterior target in GPi, we assessed the motor effects of acute electrical stimulation on different parts of the anterior GPi on parkinsonian signs and on LID in patients after implantation of quadripolar electrodes. We also evaluated the effects of chronic anterior pallidal stimulation in patients after a 6 month period.

Methods

PATIENTS

Six patients (four men, two women) fulfilling the requirements for the United Kingdom Parkinson's Disease Society Brain Bank[18] of mean age (SEM) 64 (3) years were included after acceptance of the study by the ethics committee of Auvergne University (table 1). These patients gave written consent to their participation in this study. The mean duration of the disease was 15 (2) years and the mean duration of the treatment was 12 (2) years. Before surgery, the levodopa daily dose (plus peripheral decarboxylase inhibitor) was 1200 (260) mg. Four of the patients received a dopamine

Table 1 Patient's characteristics at baseline

Patient	Age (y)	Sex	Disease duration (y)	Dosage of levodopa (mg/day)	Motor part of UPDRS		Hoehn and Yahr	
					off	on	off	on
1	73	F	13	1000	29	10	4	3
2	66	F	10	1050	41	6.5	5	2
3	66	F	20	800	42	15	4	3
4	65	F	15	1050	30	9	4	3
5	51	M	10	2500	35	7	4	2
6	65	M	25	900	38	5	5	2
Mean	64 (3)		15 (2)	1200 (260)	36 (2)	9 (1)	4.3 (0.2)	2.5 (0.2)

Values in parentheses are SEM.

agonist, one patient received tolcapone, and two patients received subcutaneous injections of apomorphine. Despite optimisation of antiparkinsonian treatment, severe motor fluctuations and monophasic and diphasic levodopa induced dyskinesias still persisted in all of the patients.

Their mean baseline unified Parkinson's disease rating scale (UPDRS) (parts I+II+III) was 60 (6).[19] All patients had an excellent response to levodopa (mean improvement 72 (33)% (table 1)). The mean duration of LIDs was 2.5 (1.0) hours and their severity was 3.0 (0.6) (items 32–33 from part IV of the UPDRS). The mean duration of daily time spent in the "off state was 1.6 (0.8) hours (item 39 from part IV of the UPDRS). All patients had no dementia (mean mental status of Folstein 28 (1). Presurgical MRI performed in the 3 months before surgery was normal.

NEUROSURGICAL PROCEDURE

A week before surgery, an MRI obtained in stereotactic conditions (sMRI) using a stereotactic frame (Leksell model G, Elekta Instruments, Stockholm, Sweden) with a repositioning system (Elekta Instruments, Stockholm, Sweden) was carried out. An iodoventriculography was also performed on the first five patients. The sMRI (Siemens Magnetom 1 Tesla, matrix 256×256) consisted of three sequences of orthogonal plans with contiguous slices 3 mm thick. T2 weighted images (TR=2500 ms, TE=20 ms) were achieved in a frontal and an axial plane and T1 weighted images (TR=450 ms, TE=15 ms) in a sagittal plane. Images were then transferred to a workstation. We used a stereotactic software package (Brainscan, Brainlab, Germany) to locate the brain structures in sMRI spaces. The target of the GPi was the vertex of the nucleus facing the knee of the internal capsule. The software calculated the coordinates of the target and the simulated electrode trajectory. A week later, the stereotactic frame was repositioned. A semi-microelectrode (FHC, Brunswick, USA) was advanced along the selected trajectory given by the software and stimulation (130 Hz, pulse width 60 µs, 0–10 mA) was performed millimeter by millimeter starting 10 mm above the target. Clinical and side effects of the stimulation were evaluated by a neurologist (FD) unaware of the stimulation condition. We used tremor, rigidity (wrist, elbow, ankle), and bradykinesia (pronosupination of the hand, thumb-index tapping) subjective assessments (improvement or aggravation percentage from the prestimulation status) to evaluate the clinical effect of stimulation. The site chosen for the definitive electrode placement was determined during stimulation by the maximum improvement of contralateral upper and lower limb tremor and rigidity, and upper limb bradykinesia. A chronic deepbrain stimulation quadripolar electrode (3387, Medtronic, Minneapolis, MN) was implanted to replace the semi-microelectrode directed toward the target. The electrode had four contacts 1.5 mm long with a distance of 1.5 mm and with an external diameter of 1.3 mm. Stereotactic *x* ray film controls were performed during the procedure to verify that there was no electrode shift. One electrode on each side was implanted during the same procedure for five patients. All patients had a postoperative MRI a week after the surgical procedure before the implantation of the programmable stimulator (Itrel II, Medtronic) in the subclavicular area.

PATIENT ASSESSMENTS

Clinical effect of postoperative acute stimulation

The effect of electrical stimulation via the four contacts of the electrode was assessed on the parkinsonian signs and on LIDs within the 12 days after the surgical procedure.

Parkinsonian signs were assessed in the off condition after interruption of the antiparkinsonian treatment for at least 12 hours using items from the UPDRS part III: contralateral limb rigidity, contralateral bradykinesia (thumb-index tapping), and contralateral upper and lower limb rest tremor. The clinical effect of electrical stimulation for each electrode (six patients, 11 electrodes) was evaluated by using improvement or aggravation percentage from clinical evaluations performed without stimulation. The LIDs were evaluated in the "on" state during two acute suprathreshold levodopa challenges on 2 consecutive days using a subjective scale (0=no abnormal movement; 4=movement resulting in severe disability) on the four limbs, on the trunk, the neck and face (maximum score 28), during rest and after an activation task (speaking aloud).[20]

The stimulation mode was unipolar with a negative electrode contact. The pulse width and the frequency of the stimulation current were respectively kept at 130 Hz and 60 µs. The voltage amplitude was progressively increased from 0 to 5 V. Clinical evaluation was performed at each voltage step. Before each assessment, a stimulation period of at least 5 minutes (parkinsonian symptoms) or at least 15 minutes (evaluation of LIDs) was used. A 10 minute period without stimulation was allowed before evaluation of another contact, showing that the clinical indices studied returned to the baseline.

Clinical effect of chronic stimulation

Patients were evaluated according to the core assessment program for intracerebral transplantation (CAPIT) protocol.[21] The evaluations, which were videotaped, were rated during the off state and during the best on state, as agreed by the patient and physician. The clinical evaluation was performed before

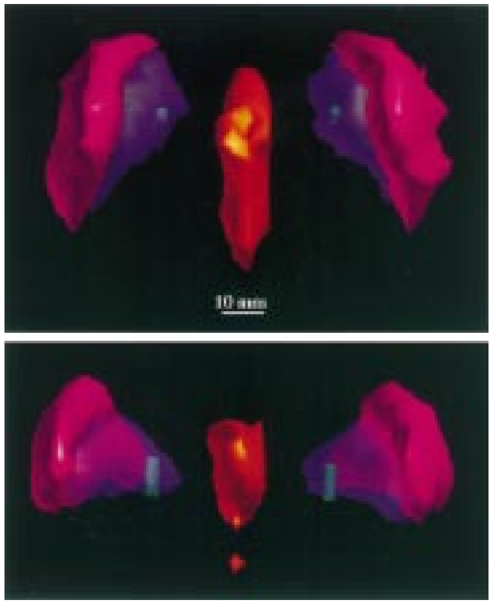

Figure 1 Three dimensional reconstruction of the right and left globus pallidus (GP) and active contacts from MRI T2 weighted images of one patient. The GP is represented by purple and the putamen by pink. The third ventricle is represented by orange. GPs are transparent to allow visualisation of the distal contacts and the active contacts (contact 2) 6 months after the surgery. Only the centre of the contacts is represented (located on the extremities of the green segments). (Upper, dorsal view; lower, posterior view.)

surgery and then on the 1st, 3rd, and 6th month in on-off drug conditions and on-off stimulation conditions. Furthermore, patients kept diaries for at least 3 days before each clinical assessment in which they noted the diurnal time spent with good motor function (on state), poor motor function (off state), and motor function accompanied by incapacitating

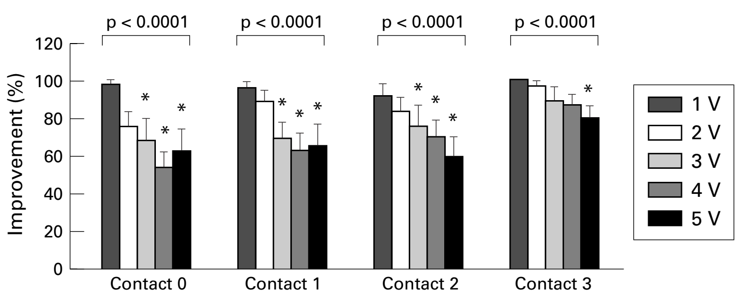

*Figure 2 Effect of acute postoperative stimulation on contralateral rigidity for each contact of electrodes (n=11); 100 % represents the rigidity score before stimulation. The effect of amplitude voltage on every contact was analysed by ANOVA with repeated measures. * p<0.05 v clinical evaluation before stimulation (Newman-Keuls tests).*

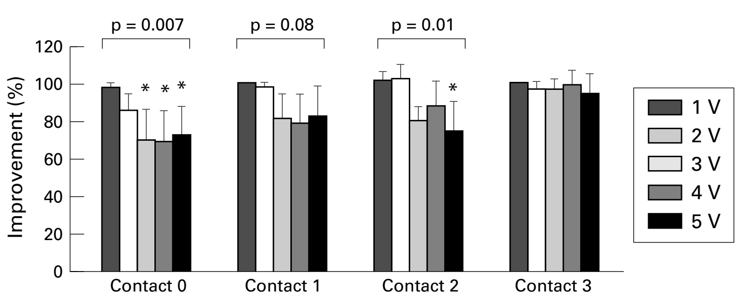

*Figure 3 Effect of acute postoperative stimulation on contralateral bradykinesia for each contact of electrodes (n=11); 100% represents the bradykinesia score before stimulation. The effect of amplitude voltage on every contact was analysed by ANOVA with repeated measures. * p<0.05 v clinical evaluation before stimulation (Newman-Keuls tests).*

involuntary movements (on state with dyskinesias). Chronic stimulation was adapted from the results that were obtained during the acute assessment period with a view to reducing the duration and the severity of LIDs, and the time spent in the off state. For each patient, stimulation indices (amplitude voltage, pulse width, frequency) were adapted every day for 2 weeks and then every month for a period of 3 months in relation with their motor status.

LOCATION OF THE ELECTRODE CONTACTS

Coordinates of the contacts which gave the best clinical results during the peroperative assessment (distal contact) and 6 months after the surgical procedure were determined from the control radiograph performed at the end of the surgical procedure. The coordinates of all contacts for the six patients were automatically placed within the pallidum, which was reconstructed for each patient in three dimensions from frontal and horizontal preoperative sMRI slices with stereotactic software (fig 1). The distances between the centre of each contact and the medial, dorsal, and ventral boundaries of the pallidum were measured for all patients (bilaterally for five patients). Furthermore, for the first five patients in which a ventriculography was performed, we also calculated the location of the distal contacts and the contacts which gave the best clinical results 6 months after the surgical procedure with reference to the ventriculographic landmarks of Talairach *et al*[22]: the laterality from the median sagittal plane of the third ventricle, the anterior position from the midpoint of the intercommissural line (Mic), and the vertical position in relation to the intercommissural line (Icl) (above or below).

STATISTICAL ANALYSIS

Values were expressed as mean (SEM). Rest tremor was not analysed because only one patient had a stable tremor in the off state. Contralateral and ipsilateral dyskinesias were calculated from the sum of the lower and upper limbs, which were items from the dyskinesia scale. The effect of the voltage amplitude for each contact electrode and for each electrode on contralateral parkinsonian signs (rigidity and bradykinesia), and on contralateral and ipsilateral LIDs, was analysed using analyses of variance (ANOVAs) with repeated measures in which the repetition factor was the voltage amplitude from 0 to 5 V. When the ANOVA showed a significant difference, the Newman-Keuls test was performed. According to the distribution of data, a Wilcoxon signed rank test and a paired Student's *t* test were used to compare assessment performed before surgery and 6 months afterwards. Significance was declared at $p \leqslant 0.05$

Results

LOCATION OF THE ELECTRODE CONTACTS

Location in relation to the boundaries of the pallidum

The mean distances (mean of both sides) from the distal active contacts to the boundaries of the pallidum were respectively to the medial

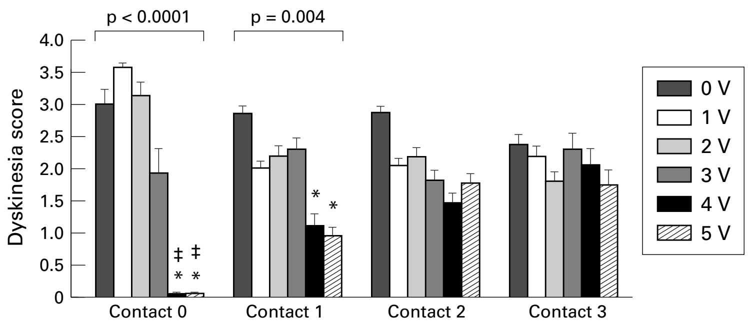

*Figure 4 Effect of acute postoperative stimulation on contralateral dyskinesia assessed during an activation task (speaking aloud) for each contact of electrodes (n=11). The effect of amplitude voltage on every contact was analysed by ANOVA with repeated measures. * p<0.05 v clinical evaluation without stimulation (Newman-Keuls tests). ‡ p<0.05 v 1 V, 2 V, and 3 V amplitude (Newman-Keuls tests).*

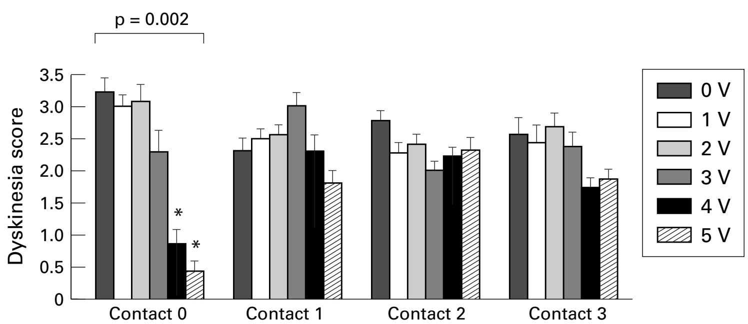

*Figure 5 Effect of acute postoperative stimulation on ipsilateral dyskinesia assessed during an activation task (speaking aloud) for each contact of electrodes (n=11). The effect of amplitude voltage on every contact was analysed by ANOVA with repeated measures. * p<0.05 v clinical evaluation without stimulation (Newman-Keuls tests).*

boundary of the pallidum 2.4 (0.7) mm, to the dorsal boundary 4.2 (0.5) mm, and to the ventral boundary 0.4 (0.4) mm. The mean distance from the active contacts 6 months after the surgery (contact 1 bilaterally in three patients; contacts 2 bilaterally (apart for one patient with unilateral stimulation) in three patients) to the boundaries of the pallidum were respectively to the medial boundary 2.5 (0.6) mm, to the dorsal boundary 2.5 (0.5) mm, and to the ventral boundary 4.2 (0.4) mm. The mean distances from the proximal contact 3 were respectively to the medial boundary of the pallidum −0.8 (1.5) mm (medial to the medial boundary), to the dorsal boundary -0.1 (0.6) mm (above the dorsal boundary), and to the ventral boundary 8.1 (0.6) mm.

Location in relation to stereotactic landmarks

For the distal contacts, the mean laterality was 15.3 (0.4) mm, the mean anterior position was 9.3 (0.6) mm in front of the Mic, and the vertical position was 0.8 (0.9) mm above the Icl. For the active contacts 6 months after the surgery, the mean laterality was 15.4 (0.4) mm, the mean anterior position was 11.5 (0.6) mm in front of the Mic, and the vertical position was 2.1 (0.3) mm above the Icl.

EFFECT OF POSTOPERATIVE ACUTE STIMULATION

Parkinsonian signs (rigidity and bradykinesia)

Analyses of variance showed a significant improvement of rigidity when stimulation was applied through the four contacts: contact 0 (distal contact), $F(8)=11.6$, p<0.0001 ; contact 1, $F(8)=9.8$, p<0.0001; contact 2, $F(8)=8.4$, p<0.0001; contact 3 (proximal contact), $F(8)=5.6$, p<0.0001. Newman-Keuls tests showed a significant improvement (p<0.05) of rigidity: (1) at 3 V, 4 V, and 5 V amplitude compared with rigidity evaluated without stimulation when electrical stimulation was applied through contacts 0, 1, and 2; (2) at 5 V amplitude when stimulation was applied through contact 3. For each contact, rigidity improved progressively with the voltage and reached a plateau at 3 or 4 V. The maximum percentage improvement decreased when stimulation was applied from contact 0 to contact 3: at optimal amplitude voltage, the rigidity percentage improvement was 47% (contact 0), 38% (contact 1), 30% (contact 2), and 20% (contact 3) (fig 2).

Analyses of variance also showed significant improvement of bradykinesia only at contact 0 ($F(8)=3.7$, p=0.007) and contact 2 ($F(8)=3.4$, p=0.01). Newman-Keuls tests showed a significant improvement (p<0.05): (1) At 3 V, 4 V, and 5 V amplitude compared with bradykinesia evaluated without stimulation when electrical stimulation was applied on the contact 0; (2) at 5 V amplitude when stimulation was applied on contact 2. At optimal amplitude voltage, the maximum improvement found was 32% (contact 0), 22% (not significant) (contact 1), and 26% (contact 2). No clinical effect was detectable when stimulation was applied through contact 3 (fig 3). An aggravation of contralateral bradykinesia by 30% was found when stimulation was applied through the four contacts with amplitude voltage higher than 3 V for two of the electrodes tested.

In one patient, stimulation on contacts 0, 1, and 2 led to a disappearance of contralateral off foot dystonia which reappeared when stimulation was stopped.

Levodopa induced dyskinesias

Analyses of variance showed a significant improvement of contralateral LIDs when stimulation was at contact 0 ($F(6)=11.1$, p<0.0001) and contact 1 ($F(6)= 4.15$, p=0.004). Newman-Keuls tests showed a significant improvement (p<0.05) of contralateral LIDs at 4 V and 5 V amplitude compared with contralateral LIDs evaluated without stimulation on contacts 0 and 1. There was also a significant improvement (p<0.05) of contralateral LIDs at 4 V and 5 V amplitude compared with 1 V, 2 V and 3 V amplitude when stimulation was on contact 0.

For all of the patients, when stimulation was applied through distal contact 0, contralateral LIDs progressively disappeared when the amplitude voltage increased with a maximum improvement of 95% at 4 V. In three patients (five electrodes), the parkinsonian signs progressively appeared and worsened when the amplitude voltage was higher than 4 V. On contact 1, the maximum improvement of LIDs was 66% at 5 V, without any worsening of parkinsonian signs. The LIDs reappeared with latency within 0 to 10 minutes when stimulation was stopped on the two lower contacts (0 and 1). No clear clinical effect was seen when stimulation was applied on contacts 2 and 3, from 0 to 5 V (fig 4).

Table 2 Stimulation indices 6 months after the surgical procedure

	Right pallidum				*Left pallidum*			
Patient	*Contact*	*Amplitude voltage (V)*	*Frequency (Hz)*	*Pulse width (µs)*	*Contact*	*Amplitude voltage (V)*	*Frequency (Hz)*	*Pulse width (µs)*
1	2	4	130	60	—	—	—	—
2	1	2.2	130	90	1	2.0	130	90
3	1	3.5	130	60	1	3.8	185	90
4	1	2.3	130	90	1	3.2	185	90
5	2	3.5	130	60	2	3.5	185	90
6	2	3.8	130	90	2	3.8	130	90

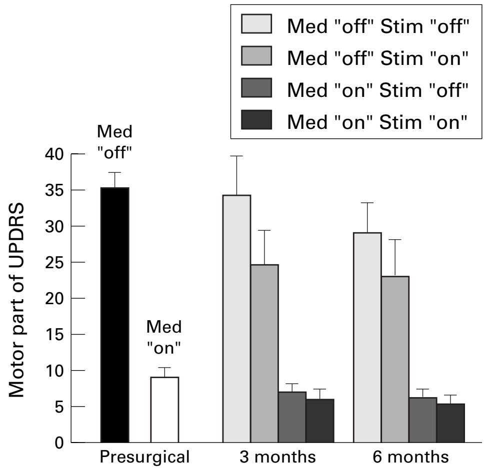

Figure 6 Effect of stimulation on motor part of UPDRS 3 and 6 months after surgical procedure (med=medication; stim=stimulation).

Ipsilateral LIDs were also improved when stimulation was applied on contact 0 as shown by ANOVAs ($F(6)=4.7$, $p=0.002$). Newman-Keuls tests showed a significant improvement ($p<0.05$) of ipsilateral LIDs at 4 V and 5 V amplitude compared with ipsilateral LID evaluated without stimulation, and at 1 V and 2 V amplitude. No significant effect was shown when stimulation was applied on contacts 1, 2, and 3 (fig 5).

Table 3 Motor evaluations at baseline and follow up 6 months after the surgery

	Medication off			*Medication on*		
		Follow up			*Follow up*	
Patient	*Baseline*	*Stimulation off*	*Stimulation on*	*Baseline*	*Stimulation off*	*Stimulation on*
1	29	43	34	10	7	6
2	41	35	32	6.5	5	4
3	42	22	8	15	5.5	3.5
4	30	19	13.5	9	6	6
5	35	37	37	7	11	10
6	38	18.5	13	5	2	2
Mean	36 (2)	29 (4) p=0.27	23 (5) p=0.09	9 (1)	6 (1) p=0.18	5 (1) p=0.13

p Values were calculated *v* evaluation at baseline.
Values in parentheses are SEM.

Table 4 Motor fluctuations at baseline and 6 months after surgery

	Baseline	*Follow up*	*p Value*
Duration of dyskinesias*	2.5 (0.5)	1.0 (0.5)	0.04
Severity of dyskinesias*	3.0 (0.3)	1.5 (0.5)	0.05
Duration of "off" period*	1.7 (0.6)	0.8 (0.2)	0.04
Duration of dyskinesias† (hours)	5.2 (0.9)	3.0 (0.9)	0.02
Duration of "best on"† (hours)	8.6 (0.5)	11.8 (0.9)	0.09
Duration of "off" period† (hours)	6.5 (0.6)	2.8 (0.7)	0.02

Values for baseline and follow up are means (SEM).
*From items of UPDRS part IV.
†Calculated from diaries.

EFFECT OF CHRONIC STIMULATION

For the 3 months after the surgical procedure, stimulation was changed from lower distal contacts to more upper proximal contacts in relation to the motor status of patients. Six months after the surgery, stimulation was applied on contact 1 for three patients and on contact 2 for the remaining three patients. The amplitude voltages were not changed compared with the effective values obtained during the acute postoperative study (table 2). Four patients reported a dramatic improvement of motor complications and two patients had a marked decrease of dyskinesia severity. Compared with preoperative values evaluated in the off condition, bilateral chronic stimulation led to a mean improvement of the UPDRS score (parts I+II+III) by 25%. The motor part of UPDRS improved by 36% (table 3, fig 6). Contralateral bradykinesia evaluated with arm movement timed tasks from CAPIT was also improved by 18% ($p<0.05$) (movements between two points), 30% ($p=0.06$) (finger dexterity), and 30% (pronation-supination; not significant). Gait disturbance improved by 20% (not significant). The mean Hoehn and Yahr staging improved by 20% ($p<0.05$). Compared with clinical evaluation performed in the on state, bilateral stimulation did not change UPDRS scores, arm timed tasks, and gait disturbance.

The mean daily duration in the off state decreased by 52% ($p<0.05$) (item 39 from the IV of UPDRS score). The mean duration of LIDs decreased by 68% ($p<0.05$) and their severity by 53% ($p=0.05$) (items 32–33 from part IV of the UPDRS score). As measured by patient self assessment, the diurnal time spent in the on state without severe LIDs increased by 37% ($p<0.05$). Similarly, the time spent in the on state with disabling LIDs, and in the off state respectively decreased by 42% ($p=0.09$) and 57% ($p<0.05$) (table 4).

There was no significant change of total daily levodopa dose (mean daily levodopa dose before surgery 1200 mg, 6 months after surgery 1275 mg) and number of levodopa daily doses. One patient stopped subcutaneous apomorphine injections.

After surgery, one patient developed a transient aseptic hyperthermia within 24 hours. Another patient developed a severe depression within the month after surgery which improved remarkably after chronic clomipramine treatment. Acute and chronic stimulation led to transient side effects such as paraesthesia, nausea, and thoracic oppression, which were mainly related to the amplitude voltage. Postoperative MRI was normal.

Discussion

EFFECT OF POSTOPERATIVE ACUTE STIMULATION

In this study, postoperative acute electrical stimulation in the anterior GPi induced a marked improvement of cardinal parkinsonian signs (akinesia and rigidity) when patients were in the off state, and led to a dramatic decrease in severity of contralateral and ipsilateral LIDs when patients were evaluated in the on state. At a higher voltage, blockage of the levodopa effect leading to reappearance of parkinsonian signs was found in three patients, as already reported by Krack *et al*[13] The effect of stimulation on rigidity, bradykinesia, and on LIDs predominated when stimulation was applied on the ventral contacts, and then progressively decreased when stimulation was applied on the dorsal contacts.These results are at variance from those of Bejjani *et al*[23] who reported that acute stimulation in the posteroventral GP, using the same electrode as in our study, had a striking, different effect on parkinsonism and dyskinesia when applied to two different targets of the GPi. The stimulation on the dorsal part of the Gpi led to an improvement of parkinsonian signs when patients were in the off state whereas stimulation applied on the ventral part of the GPi led to a worsening bradykinesia when patients were in the off state, but suppressed LIDs when patients were in the on state. Krack *et al* also reported that stimulation on the ventral part of GPi induced an improvement of rigidity whereas stimulation on the dorsal part led to a moderate improvement of akinesia.[13]

Our different results could be explained by the fact that we have implanted electrodes more anteriorly and medially in the GPi. The volume of neural tissue affected by stimulation is probably in the order of mm^3. Thus, the effect of stimulation probably predominates in the anteromedial part of the GPi although the diffusion of current can also slightly influence the posteroventral part. In our study, the distal contacts were on average 6 mm in front of, 6 mm above, and 5 mm medial to the target of Laitinen *et al*,[2] and thus corresponds to the classic anterior target for pallidotomy.[15] Furthermore, according to the stereotactic coordinates of Talairach *et al*,[22] the active contacts projected into the internal part of the GPi, and into the ansa lenticularis. Moreover, the superimposition of active contacts within the pallidum showed that the electrodes are placed in the anteromedial part of the pallidum. According to the distances from the contacts to the boundaries of the pallidum on one hand, and the size of the GPi on the other,[24] it may be assumed that the distal contacts were on the ventral boundary of the GPi and the contacts 1 and 2 were within the GPi (fig 1). The fact that stimulation on the proximal contact 3 does not induce any significant change of bradykinesia and LIDs, relates to their anatomical location, situated above the Gpi in the anterior part of the internal capsule.

The anteromedial part of the GPi, which corresponds to the ventral pallidum, is crossed by a greater number of fibres at the origin of the outflow pathways, given the convergence of the anatomical structure to GPi output. These pathways (ansa lenticularis, lenticular fasciculus) are mainly localised above the optic tract and medially to the pallidum and project to the thalamus throughout the internal capsule.[25] Thus, stimulation on the distal contact probably influenced the ansa lenticularis, which was localised on the ventral surface of the pallidum.

Although the effect of electrical stimulation is largely unknown, it is assumed that stimulation induced a direct or indirect neuronal inactivation, as shown by electrophysiological studies in rats.[26] The improvement of parkinsonian signs by stimulation on the distal contact when patients were in the off state may be explained by inhibition of the GPi, which is hyperactive after the striatal dopamine depletion seen in Parkinson's disease. The decrease of GPi activity disinhibits the pallidal relay nuclei of the thalamus, which leads to a disinhibition of thalamocortical neurons resulting in an improvement of parkinsonian signs.[27–29] Such results have been shown in PET studies in parkinsonian monkeys and in parkinsonian patients in which pallidal stimulation and pallidotomy restore the regional cerebral blood flow in the frontal cortex.[30 31] Otherwise, the improvement of LIDs by stimulation on the distal contact is hard to explain by the classic model of the basal ganglia because LIDs may be considered to be linked to GPi hypoactivity.[32–34] However, a recent electrophysiological study performed on parkinsonian monkeys with dyskinesias suggests that dyskinesias could also result from an imbalance of neuronal activity within the GPi, where hypoactive neurons were surrounded by hyperactive or unresponsive neurons.[35] Thus stimulation of the medial GPi could reestablish a normal balance of activity between the different neuronal networks in the GPi leading to an improvement of LIDs.

EFFECT OF CHRONIC STIMULATION

In our study, chronic stimulation in the anterior GPi led to an improvement of parkinsonian signs and LIDs. Furthermore, stimulation significantly increases the daily duration of the on state and reduces the time spent with severe dyskinesias in this state. Moreover, stimulation significantly reduces the time spent in the off state. The fact that our chronic results are close to those reported in other studies in which stimulation was in the posteroventral portion of the GPi, suggests that the anterior target could be as effective as the posteroventral part of the GPi in advanced Parkinson's disease.[11–13] Compared with the ventrolateral GPi, one of the advantages of the anterior target is that it is easily located by using stereotactic MRI.

Compared with the clinical effect found during the acute assessment, the best results of chronic stimulation occured when stimulation was applied on more proximal contacts, which were more dorsal than the distal contacts. One of the possible explanations could be that chronic stimulation on the distal contacts when patients are in the on state decreases

LID but also induces a blockage effect of levodopa at a lower voltage than during the acute evaluation, requiring stimulation to be moved to the proximal contacts. These results could indicate that the stimulation condition (acute *v* chronic) leads to different changes in the activity of GPi or alternatively induces tolerance phenomena.

In our study, there was no permanent morbidity associated with the surgical procedure. The side effects were in relation to the stimulation condition and always reversible by the reduction of the amplitude voltage. Such results have been reported in other studies showing that the procedure of chronic pallidal stimulation is neurologically safe[36–38] compared to the pallidotomy in which the incidence of long term complications was noted in 10% in a study comprising 138 patients.[39]

Our chronic results are close to those reported when chronic stimulation was applied in the posteroventral part of the GPi, in which reduction of the motor score of UPDRS by 30–40% and an improvement of dyskinesia by 60–70% was found.[37 38] However, chronic stimulation of the subthalamic nucleus could give better results than stimulation of GPi whatever the site of stimulation because a recent retrospective study comparing stimulation of subthalamic nucleus or GPi (posteroventral part) in young patients has shown a significant higher improvement of the motor score of the UPDRS, and a significant reduction of treatment when stimulation was applied on subthalamic nucleus.[38] However, such a result needs to be confirmed by randomised trials.

In summary, acute anteromedial GPi stimulation applied to the distal part of the nucleus induces an improvement of parkinsonian signs when patients are in the off state and of dyskinesia when they are in the on state. Chronic results show that this is an effective treatment for advanced Parkinson's disease with benefit sustained for at least 6 months, which suggests that the procedure will be effective for years. A survey of patients every 6 months is now in progress. However, this surgical procedure needs to be evaluated with a larger number of patients and to be compared with other neurosurgical treatments such as ventrolateral GPi and subthalamic stimulations.[38 40–43]

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HISTORICAL NOTE

Some contributions of Duchenne de Boulogne (1806–75)

PROGRESSIVE MUSCULAR ATROPHY

In 1849 Duchenne described a patient with spreading progressive muscular atrophy that started in the hands and spread slowly to the arms and legs, with no sensory signs, pain, or sphincter disturbance. Characteristically self effacing, he did not publish the case himself, but passed on his observations to François Amilcar Aran, physician to the Hôpital Saint Antoine. Aran published the paper[1] and acknowledged: "I owe a thousand thanks to my friend Duchenne de Boulogne who freely put at my disposal all his material . . ."

Duchenne's account (translated by G V Poore) followed in 1870[2]: "Muscles . . . often jerked by little fibrillary or partial contractions . . . agitated with worm-like movements. Progressive muscular atrophy attacks the upper limbs, and destroys its muscles in an irregular fashion. It begins in such cases by attacking one after another the muscles of the thenar eminence, spreading from the superficial to the deep layer. As soon as the abductor pollicis is wasted, its absence is marked by a depression, and by the attitude, during repose, of the first metacarpal bone, which lies too close to the second . . . Depressions of the hypothenar eminence and interosseal spaces next announce the atrophy of the muscles of those regions. The loss of the interossei muscles is shown by the claw-like attitude of the fingers . . . The atrophy may remain localised for many years . . . The flexors of the elbow and the deltoid are the first to atrophy. The triceps extensor cubiti is the last of the muscles of the upper limb to become affected. . . . Whenever all muscles of the arm have been atrophied, I have found a greater or lesser number of muscles of the trunk in the same condition . . . first, the lower half of the trapezius . . . I have usually seen the muscles of breathing and swallowing become affected. The atrophy equally invades the lower limbs, but only when the muscles of the upper limbs and trunk are in great part destroyed. It is most marked in the flexors of the ankle and hip. I have not seen atrophy attack both sides at once, but when one muscle is affected the corresponding muscles are usually attacked at no distant time."

He also wrote: " . . . (I have) only seen it begin in the lower limbs . . . twice out of 159 cases . . . in a good third of cases that electromuscular sensibility, as well as cutaneous sensibility was more or less weakened . . .. (There are) "change of form and attitude," superficial deformities, "functional troubles during voluntary action," and he notes the "wasting of intercostals and diaphragm . . . a great hindrance to breathing, and still more to phonation . . . there is no paralysis of the bladder or rectum . . . Duration.—This is very variable. The diseasemay reach its last stage in less than two years . . . I have seen it in this way remain localised for some eight or nine years . . . Electromuscular contractility is normal- . . . beyond doubt."

Pathologically, Duchenne reported the loss of striation, replacement by granular matter and fat vesicles, and fascicular atrophy of the muscles. But, he prefaces his account by saying that: "the feebleness of contractility . . . is chiefly the consequence of the wasting, . . . and not the result of paralysis, i.e. of a failure of the motor nerve action."

MUSCLE DISEASE AND "DUCHENNE'S DYSTROPHY"

His investigations of muscle disease continued with his invention of the "harpoon" that he employed to perform percutaneous muscle biopsies; not surprisingly, this aroused hostile criticism of its ethical propriety in the local press. The discovery of pseudo-hypertrophic paralysis, or myo-sclerotic paralysis in 1868,[3] was however, a remarkable and important contribution, dependent on and illustrated by pictures of histology obtained by harpoon biopsy: "This disease is mainly characterised: 1. By feebleness of movement, usually situated at first in the muscles of the lower extremities and of the lumbar spine, ultimately spreading progressively to the upper limbs, and increasing in intensity till all movement is lost; 2. increase in size of most of the paretic muscles; 3. By increase of the interstitial connective tissue of the paretic muscles, and in the more advanced stages by an abundant production of fibrous tissue or of fatty globules. The name I have given to this disease pseudohypertrophic muscular paralysis . . . has reference to the symptoms . . .. It may be called myo-sclerotic paralysis, a name which is more scientific and justified by pathological anatomy."

Of his many other contributions were original descriptions of the use of photography of microscopic histology, tabetic locomotor ataxia which contemporaries had confused with Friedreich's disease, the anterior horn cell lesions, which caused acute poliomyelitis, and glossolabio-laryngeal paralysis (bulbar palsy).

Guillaume Benjamin Amand Duchenne[4] was the son of a long lineage of seafarers and fishermen in the region of Boulogne sur Mer. According to Laségue and Strauss, he was of the middle height, thickset, active in movement, slow of speech and retaining to the last a faint provincial accent. He studied medicine in the University of Paris, under Laennec, Cruveilhier, and Dupuytren. He graduated in 1831. He returned to Boulogne to a limited private practice, but was badly affected by his young wife's death in childbirth. He lived only for his patients and for his scholarship.

Lonely and isolated from his friends, he returned to Paris in 1842 and started to experiment with Faradic current on the function of skeletal muscle. He sought no formal appointment, but attended patients in many Parisian hospitals, questioning and examining patients with laborious obsession, often following their progress by visiting them in their homes for many years. At times, he was humiliated by established physicians: "the monarchs of the wards", he called them. His reputation slowly increased, despite a neglect of pathological anatomy, and his dependence on his own observations rather than on neurological writings. Later in life he concentrated more on the nervous system than on muscles, taking up histology with youthful zest. Both Charcot and Trousseau fostered his recognition and showed him great respect: Charcot's lectures contain frequent acknowledgement of his work.

Neither succinct as a writer, nor systematic in his work, his lengthy papers emerged slowly. His first, *L'Electrisation Localisée et de son application à la pathologie et à la thérapeutique*, was published in 1855, was well received, and encouraged more research and trials of electrotherapy; by 1872 it had achieved a third edition.[2] In 1862 his previously estranged son joined him in Paris. He started, at last, to gain international respect. This culminated in election to many medical societies throughout Europe. A final disaster occurred when his son died of typhoid fever in 1871, with grave and lasting effects on his personal life. He died of a cerebral haemorrhage in 1875.

His epitaph we can leave to Charcot who remarked : "How is it that one fine morning Duchenne discovered a disease that probably existed in the time of Hippocrates? Why do we realise things so late, so poorly, with such difficulty . . ..Because our minds have to take in something that upsets our original set of ideas . . ." A bas-relief in the Salpêtrière shows the doctor attending his patient, applying electrodes attached to a simple generator. The accompanying plaque reads:

> A. Duchenne (de Boulogne)
>
> Electrisation Localisée
>
> Physiologie des Mouvements
> Neuropathologie

Postscript: Edward Meryon (1807–) presented a paper to the Royal Medico-chirugical society on 9 December, 1851, which described two typical "Duchenne" families and one with Becker type dystrophy. He recognised them as primary diseases of muscle[5] and showed postmortem the typical "granular degeneration"[6]

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