

Surgical treatment for Parkinson disease

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Introduction

Since the beginning of neurosurgery, operations have been carried out throughout the central nervous system to treat movement disorders. In the 1930's and 1940's, early neurosurgical procedures focused on pyramidal tract lesions for tremor resolutions, but tremor reduction came only at the expense of motor weakness. The era of basal ganglia surgery for Parkinson's disease (PD) began when Meyers first noted that ablation of pallidofugal fibers, originating from the medial globus pallidus improved tremor and rigidity. Unfortunately, the reduction of symptoms was often accompanied by neurological deficit. Another technique, the ligation of the anterior choroidal artery was found by accident. Cooper while performing a pedunculotomy in order to treat a postencephalitic parkinsonian patient tore inadvertently the anterior choroidal artery and had to ligate the vessel. Without pedunculotomy, the tremor and rigidity was considerably reduced without paresis. He performed this procedure in 55 patients with abolition of tremor in about 65%, and reduction of rigidity in 75% while creating a hemiplegia in 11% and having an operative mortality of 10%.

Pallidotomy became a popular surgical procedure in the 1950's. Spiegel and Wycs, the pioneers of this new technique carried out a pallidotomy in 50 patients improving tremor in 78% with an operative mortality of 2,8% and permanent hemiplegia in 4% of their cases.

Thalamotomy eventually replaced pallidotomy as the treatment of choice because of more consistent benefit in tremor reduction and lower rates of tremor recurrence. However, the side effects of thalamotomy included motor deficits and dystonia; and bilateral thalamotomy often resulted in dysarthria and neuropsychiatric complications. Bilateral lesions in the thalamus are therefore nowadays considered to be contraindicated.

The development of L-Dopa in the early 1960's and its clinical introduction in 1967 was responsible for a steep decline in functional stereotactic procedures, especially in patients with PD. L-Dopa still remains today the most effective treatment for PD. Providing initially dramatic relief of symptoms, motor fluctuations and dyskinesias, a diminished response to the drug after 5-10 years is likely to occur.

Nowadays surgical options to treat PD include lesioning (thalamotomies and pallidotomies), deep brain stimulation (nucleus ventralis intermedius of the thalamus, internal segment of the globus pallidus and subthalamic nucleus) and implantation of cells into a target site attempts to replace neurons that have died from disease process.

[1] EFFECTS OF ANTERODORSAL PALLIDAL STIMULATION ON GAIT FREEZING (KINESIA PARADOXA) IN PARKINSON'S DISEASE. STEREOTACT FUNCT NEUROSURG 2000; 74: 99-105

Information

The authors present the results of a double-blind evaluation of the effects of internal globus pallidus (GPi) stimulation in 7 patients with advanced Parkinson's disease. The patients were subjected to two sessions of 1 day evaluation. Before the day of evaluation, the stimulation was turned on in the morning by the physician. The patients were maintained on-stimulation thereafter, and assessed periodically during their daytime activity by the rating physician. One to two weeks after the initial evaluation, the patients were assessed by the same rating physician in an identical manner while being maintained off-stimulation. The order of assessment with on and off stimulation was determined randomly. Neither the rating physician nor the patient was informed as to the status of the stimulation. Although many patients could recognize whether the stimulator was turned on or turned off from their symptoms, they were prohibited from informing their inference to the rating physician.

During the evaluation, the patients were on medication with a dose and schedule which were thought to be optimal for each patient. The best and worst scores during their daytime activity were recorded as the on-period score and off-period score, respectively, excluding the condition where the patient woke up in the morning.

A significant reduction in the total score on part III of the UPDRS (United Parkinson's Disease Rating Scale), was induced by GPi stimulation at the off-period (-57%) as well as the on-period (-36%). Clinically important improvements were also achieved in severe gait freezing in 2 patients when stimulation was applied to the anterodorsal portion of the GPi. Such an effect was observed during unilateral stimulation of the right side alone.

Analysis

Chronic high-frequency stimulation of the GPi has been shown to improve off-symptoms, dyskinesias, rigidity and tremor. Due to the large size of GPi, its somatotopy and vicinity of important structures as the internal capsule and the optic tract, microelectrode recordings are recommended by most groups. The authors make a double blind evaluation of the effects of GPi stimulation performed 6-8 months after surgery in 7 patients with PD; The evaluation revealed that the total score on part III of the UPDRS at on-stimulation was significantly lower than that at off-stimulation in both the off-period (43.1±8.8 vs. 18.7±5.7; -57%; $p < 0.002$) and the on-period (19.7±3.3 vs. 12.1±5.2; -35%; $p < 0.02$).

This study demonstrated that the GPi stimulation improves the symptoms of the PD (in this case principally in rigidity), and reduced significantly the total score on part III of the UPDRS. In addition, the authors indicated that clinically important improvement in gait freezing can be achieved when stimulation is

applied to the anterodorsal portion of the GPI. In our opinion further clinical studies are necessary to confirm this affirmation.

[2] PALLIDOTOMY MICROELECTRODE TARGETING: NEUROPHYSIOLOGY-BASED TARGET REFINEMENT.

Neurosurgery 2000; 46: 613-624

Information

This paper analyses the track physiological factors that seem most significant in determining the microelectrode recording tracks that will be chosen for pallidal lesioning. Thirty six patients with PD underwent microelectrode guided pallidotomy. Between one and five microelectrode recording tracks were made per patient. Usually one or two of these tracks were lesioned. Electrode positions in the x and y axes were recorded and related to track neurophysiological findings and final lesion locations. The stereotactic location and sequence of microelectrode tracks were recorded and plotted to illustrate individual search patterns. These patterns were then compared with those noted in other patients. Neurophysiological data obtained from recording tracks were analyzed. A retrospective analysis of track electrophysiology was performed to determine the track characteristics that seemed most important in the surgeons' choice of the track to lesion. Orthogonally corrected postoperative magnetic resonance images were used to confirm the anatomic lesion location.

Basic physiological elements of each electrode track were recorded (neuronal activity, kinesthetic, visual and tremor synchronous firing). Track trajectories containing all of these characteristics were given a higher rank than other trajectories.

Anatomic analysis, using postoperative magnetic resonance imaging, revealed that all lesions were placed in the globus pallidus. Most patients (35 of 36) improved after surgery.

Analysis

The Pallidotomy was resurrected in the 1980's for Laitinen et al. The advances in stereotactic techniques, improved neuroimaging and a better understanding of the anatomy of the basal ganglia motor circuit led to resurgence of the procedure in the 1990's. Pallidotomy (the lesion of the GPi), is very effective in reducing contralateral tremor, rigidity, bradykinesia and dyskinesia. But, because the optic tract and internal capsule lie in close proximity of the GPi, potential complications like visual field deficit and hemiparesis may occur.

The authors analyzed in this study, the physiological track that seemed most significant in determining the microelectrode recording tracks that would be chosen for pallidal lesioning.

Four basic elements of electrode tracks were recorded: a) general neuronal activity; b) tremor synchronous cells; c) visually active cells; d) joint responsive cells.

Track trajectories containing all of these elements were lesioned 85% of the time (20 of 24 patients). The level of electrophysiological activity in the first track was the best predictive factor in determining whether the next microelectrode move would be closer to the ultimately lesioned track. The analysis of electrode track location and neurophysiological properties yields useful information regarding the effectiveness of microelectrode searching in the x and y axes. This is a very interesting and illustrative article to show the value of microelectrode recording in functional neurosurgery.

[3] TEMPORAL SEQUENCE OF RESPONSE TO UNILATERAL GPI PALLIDOTOMY OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE.
STEREOTACT FUNCT NEROSURG. 2000; 75: 160-166.

Information

Globus Pallidus Internus (Gpi) pallidotomy, is one of the therapeutic options for patients with medically intractable Parkinson's Disease (PD). A surgical lesion produced in the posterior third of the Gpi, improves the cardinal symptoms of PD, as well as levodopa-induced dyskinesias. The present study was performed to determine the temporal sequence of the response to unilateral MRI / microelectrode-guided pallidotomy of each cardinal symptom in PD. For this purpose, 19 consecutive patients (10 females and 9 males), were underwent to an unilateral Gpi pallidotomy for medically intractable PD. Their mean age was 63.4 years and mean disease duration was 11.8 years. In all patients, the surgery was performed contralateral to the more severely parkinsonian side. There were 9 left side and 10 right side surgeries. Posterior Gpi pallidotomy was carried out using an MRI / microelectrode-guided technique with selective third ventriculography. The optimal target was determined 2mm anterior and 20 mm lateral to the midpoint of the intercommissural line, and 1mm dorsal to the third ventricle floor. An electrical stimulation with a monopolar radiofrequency probe was performed prior to lesioning to prevent injury to the internal capsule or optic tract.

Compared with the baseline, the total motor UPDRS at 6 months after surgery was significantly reduced in both, the "off" ($p= 0.001$) and "on" ($p= 0.005$) states. The mean UPDRS motor score in the "off" state decreased from 49.8 at baseline to 29.4 at 6 months; and in the "on" state it decreased from 31.1 at baseline to 22.6 at 6 months. This represents a mean improve of 41% in the "off" state and 23% in the "on" state 6 months after the operation. In this paper the authors report that although all the motors signs, were significantly improved 6 months after pallidotomy, the temporal sequence of tremor response was different from those of others symptoms.

Analysis

Since 1987, and especially since Laitinen's publication of 1992, pallidotomy has had a very favorable reception in the United States. The revival of this technique is related to the fact that long term treatment with L-Dopa has led, in many patients, to the development of a rapidly debilitating clinical syndrome

characterized by rapid and unpredictable alteration of severe parkinsonian symptoms, including akinesia, freezing, iatrogenic dyskinesia and hiperkinesia. The pallidotomy (lesion of the Gpi), is very effective in reducing contralateral tremor, rigidity, bradykinesia, and dyskinesia. But, because the optic tract and internal capsule lie in close proximity of the Gpi, potential complications, like visual field deficit and hemiparesis, may occur. The incidence of these complications can be significantly reduced by electrophysiological exploration of the target area. Moreover, improved MRI sequences can obviously provide very accurate localization of the target and also minimize the risk of adverse effects.

This study shows that 6 months after unilateral Gpi pallidotomy, all cardinal symptoms of PD were alleviated, resulting in a significant improvement in total UPDRS "off" motor scores. The operation also improved the total UPDRS "on" motor scores; while the UPDRS akinesia scores were not significantly reduced in the "on" state. It appears that the temporal sequence of response to pallidotomy of tremor is different from those of other symptoms. Among cardinal signs, only tremor showed a bipolar alleviation pattern. The mean UPDRS tremor score was reduced from 4.8 +/- 2.2 at baseline to 2.5 +/- 1.2 three days after surgery ($p=0.005$). Thus, contralateral tremor was significantly improved immediately after pallidotomy. However, it returned to the preoperative baseline level, one week after surgery and lasted for another week: the mean tremor scores one and two weeks after surgery were 4.1 +/- 2.0 ($p<0.005$ vs 3 days; $p>0.05$ vs baseline); and 4.0 +/- 1.9 ($p<0.005$ vs 3 days; $p>0.05$ vs baseline), respectively. Thereafter, the UPDRS tremor score again declined gradually during a one month period (2.4 +/- 1.2; $p<0.005$ vs 2 week) and over a 3 month period (1.3 +/- 0.6; $p<0.005$ Vs 1 month) after surgery, and lasted for another 3 months. Thus, the tremor-alleviating profile during the postoperative course appeared to be biphasic. The authors postulate that this phenomenon may be due to the transient functional alteration in a network associated with PD tremor by surgical stress that might fade away within a week after surgery. We believe that more studies must be made to confirm this interesting mechanism.

[4] A COMPARISON OF SURGICAL APPROACHES FOR THE MANAGEMENT OF TREMOR: RADIOFREQUENCY THALAMOTOMY, GAMMA KNIFE THALAMOTOMY AND THALAMIC STIMULATION
STEREOTACT FUNCT NEUROSURG. 1999; 72: 178-184

Information

The authors show the results of 39 stereotactic procedures made between 1994 and 1999, for patients with intractable tremor. A retrospective analysis of results of radiosurgical thalamotomy ($n=15$), IRM guided stereotactic radiofrequency thalamotomy ($n=13$), and deep brain thalamic stimulation (DBS; $n=11$) was performed to study relative advantages and risks of these procedures. Despite all the options were discussed with the patients, radiosurgery was usually performed on elderly patients with concurrent medical problems. Stereotactic thalamotomy and DBS was performed with IRM guidance and macrostimulation. The choice between thalamotomy, DBS and radiosurgery was not randomized. Of the 15 patients who chose Gamma Knife thalamotomy, 9 had associated medical problems, 3 had recurrence following previous successful stereotactic

thalamotomies and 1 was a 92 year old. The other 2 patients had multiple sclerosis with violent disabling tremor and underwent radiosurgery in order to minimize the patient participation during the surgery. For radiosurgery, a median dose of 140 Gy (range 130-150 Gy) was delivered using a single 4 mm collimator.

Five of the 13 patients who underwent radiofrequency thalamotomy had complete arrest of tremor, 6 had a significant reduction and 2 had approximately 50% reduction intraoperatively. Long term follow up showed continued excellent tremor control in 5 (38.5%), and partial relief in 2 (15.4%). Six patients experienced return of tremor to near baseline; 3 of these patients finally underwent a Gamma Knife thalamotomy with the aim of enlarging the lesion and 1 was managed by DBS.

All 11 DBS patients had excellent control of tremor immediately after the procedure. Although all of these patients required parameter changes, long-term follow up showed that 9 of 11 maintained excellent tremor control.

Of the 15 patients who underwent radiosurgery, one died due to unrelated causes after 6 months. Radiosurgical thalamotomy was effective in all 12 patients who had more than 6 months follow-up. Ten patients (83%) noted excellent relief (3 had complete arrest and 7 had 90-95% improvement) and 2 (16.7%) had good relief. The onset of tremor relief varied from 1 to 6 months (median = 2 months).

Analysis

In this paper, the authors show that immediate results are equally good with radiofrequency thalamotomy as with thalamic DBS. However, the recurrence of tremor could be more easily managed by changing the parameters of the pulse generator in patients with thalamic DBS. In all but 1 patient, control remained well within the capacity of the stimulator. In long term follow up, complete or near complete relief of tremor was maintained in 50% of patients with essential tremor and 40% of patients with parkinsonian tremor in the radiofrequency thalamotomy group, in 83% of patients with essential tremor and 50% of the patients with parkinsonian tremor in the thalamic DBS group, and in 80% of patients with essential tremor and 100% of patients with parkinsonian tremor in the radiosurgical thalamotomy group.

The thalamotomy yields excellent results, particularly in cases of typical parkinsonian tremor. The morbidity is near 1%, and permanent functional sequelae occurred in approximately 7%. Therefore, despite the radical nature of this treatment when compared to the more conservative, like reversible technique of stimulation, thalamotomy deserves to retain an important role in the treatment of medically intractable PD, when the dominant symptom is the unilateral tremor (no rigidity, akinesia or dyskinesias where we preferred pallidal or subthalamic stimulation). Thalamotomy does not require repeated follow up and tuning of equipment, in contrast, thalamic DBS necessitates frequent visits. Thalamic DBS is a totally conservative and reversible technique, mandatory when thalamotomy is contraindicated, such as in patients who have undergone a previous contralateral thalamotomy on the non dominant side. It is known that bilateral thalamotomies have a significantly high rate of complications. In comparison, thalamic DBS does not have severe complications, and it offers the

additional advantage, that stimulation is adjustable and the adverse effects are reversed when stimulation intensity is decreased.

Although thalamotomy and thalamic DBS may be performed under local anesthesia, there are a group of patients who have conditions that predispose them to a high risk from invasive procedures. This group includes patients who are on anticoagulant therapy, have advanced respiratory or cardiac disease or are very old. For these patients who cannot tolerate an open stereotactic procedure, the Gamma Knife Thalamotomy may represent the only therapeutic option.

[5] STEREOTACTIC VENTRAL INTERMEDIAL THALAMOTOMY FOR THE TREATMENT OF ESSENTIAL TREMOR
STEREOTACT FUNCT NEUROSURG. 1999; 72: 174-177

Information

Essential tremor (ET) is the commonest movement disorder that has prevalence between 0.4 and 4% in general population and between 1.3 and 5% in those over the age of 60 years. Conservative management of ET is limited to several pharmacological agents (propranolol, primidone), but if these drugs do not reduce tremor and functional disability, surgical management is the next option.

In this paper, 37 patients with intractable ET have undergone stereotactic ventral intermedial (VIM) thalamotomy. Twenty four patients (64.9%) were male. The age varied from 42 to 84 years (mean 70.9 years), and the mean duration of the symptoms was 33.3 years. The diagnosis of ET was based on the patient's symptoms, family history and neurological evaluation. The surgery in all cases was performed with stereotactic technique using MRI or CT localization. Intraoperative neurophysiological confirmation of the target location was obtained using a macrostimulation technique. All the patients experienced either complete abolition of the contralateral tremor or significant improvement in tremor intensity immediately after surgery. At the follow up examination, 13 months after the operation, 60.5% of patients had no tremor, and 13.9% had mild residual tremor without interference with daily life. Tremor recurrence was observed in 5 patients, all of whom underwent repeat VIM thalamotomy with excellent results. Transient problems with speech and motor functions were observed after 15 thalamotomies, permanent hemiparesis and speech difficulties were seen in 6 patients.

Analysis

Essential tremor is a relatively common movement disorder, affecting 415 per 100,000 persons older than the age of 40 years. It is marked by a low frequency tremor (4 to 8 Hz) that is precipitated by volitional movement, but often disappears on repose. The tremor preferentially affects the upper extremities, with the head and lower extremities affected to a lesser extent. Although the origin of the phenomenon is not well understood, a familiar form of the disease does exist. It is transmitted in an autosomal dominant pattern with high penetrance in such cases. Surgical treatment of essential tremor is indicated

when conservative management fails to relieve tremor or improve functional status of patients. Two currently available surgical techniques for tremor are stereotactic VIM thalamotomy and VIM thalamic DBS. The thalamotomy procedure was developed almost 50 years ago and is currently considered a treatment of choice for unilateral or predominantly unilateral tremor. Mohadjer et al. Reported on 105 patients with essential tremor operated on between 1964 and 1984 at the University of Freiburg, Germany. The anatomic target was the zona incerta either alone or in combination with other target points. These surgeons reported a 93.7% improvement in tremor control in the immediate postoperative period. A follow up questionnaire was sent to all 105 patients, with a mean follow up period of 8.6 years. Of the 65 patients who responded, 68.7% believed that they were still enjoying a significant benefit from the surgery, however, nine patients experienced persistent side effects. Five patients had contralateral weakness, one had dysarthria, and three showed signs of cerebellar dysfunctions. The primary alternative to stereotactic VIM thalamotomy for essential tremor is the implantation of DBS into the VIM. It has long been known that electrical stimulation can inhibit tremor. The effect is immediately reversible when the stimulation is discontinued and is obtained only at high frequencies (100 Hz and higher). Due to of the concerns of side effects and complications associated with bilateral ablative surgery, Benabid et al. initially proposed the used of chronic DBS for patients who had thalamotomy on one side and who requested the procedure on the contralateral side. Furthermore, DBS can be adapted to tailor the stimulation patterns to match the patients' symptoms and clinical concerns. By reducing, modifying or stopping stimulation, unpleasant or disabling side effects can be reduced or eliminated.

The authors' results correlate with those reported in the literature. We think that stereotactic VIM thalamotomy is a very effective procedure for medically intractable unilateral essential tremor.

[6] SUBTHALAMIC STIMULATION IN PARKINSON'S DISEASE
STEREOTACT FUNCT NEUROSURG 1999; 72: 170-173

Information

The authors wanted to evaluate chronic subthalamic nucleus (STN) stimulation as an alternative to pallidotomy for severe Parkinson's disease symptomatology. For this reason 9 consecutive patients who met the criteria for functional neurosurgery were included in this study. All had severe medically refractory drug-induced dyskinesia and had reached maximal daily levodopa therapy. All parkinsonian patients had pre and postoperative UPDRS III scores, dyskinesia scores, neuropsychometric studies and videotaping. Three patients were selected to undergo stereotactic implantation of a subthalamic deep brain stimulation (DBS) after Institutional Review Board approval and informed consent. These were performed using digitized microrecordings. The other group received unilateral pallidotomy. Postoperatively, the clinical results demonstrated a significant improvement in the overall UPDRS scoring. The "off" motor scores improved the most, up to 22% in the pallidal group vs 32% in the STN group. In addition, the contralateral "on" dyskinesia improved by 66% of the pallidotomy group vs 80% in the STN stimulation group. The levodopa therapy, decreased by

50% in the STN stimulation group only. In this work, the authors concluded that chronic stimulation of the STN appears to provide significant motor improvement in patients with severe Parkinson's disease and is more beneficial than pallidotomy.

Analysis

Unilateral Gpi pallidotomy reduces bradykinesia, rigidity and tremor, mainly on the contralateral side, but also ipsilaterally. One of the most dramatic effects of the surgery is the almost complete elimination of L-Dopa induced involuntary movements on the side contralateral to the lesion. The improvements are immediate. The microelectrode recorded-guided technique has allowed accurate lesion placement and has made possible the avoidance of visual and corticospinal complications. The optimal lesion side and site within Gpi remain to be determined. It is obviously desirable to make as small a lesion as possible, but the lesion has to be large enough to accomplish the purpose for which the surgery is done. Gpi has not only motor functions but also limbic and associative territories and functions. This indicates that changes in cognitive function may be associated with Gpi lesion. Which population of Gpi neurons or pallidofugal axons should be targeted to obtain the maximal motor benefit while minimizing the risk of adverse effects remains to be determined. Although there are bilateral benefits from unilateral pallidotomy, certain patients continue to have disabling ipsilateral and axial motor dysfunction after surgery. Bilateral pallidal surgery is possible, but is associated with an increased risk of complications including cognitive and bulbar symptoms, especially dysarthria and swallowing difficulties. An alternative to bilateral lesion surgery may be the use of chronic high-frequency electrical deep brain stimulation (DBS) on one or both sides. Siegfried and Lippitz first reported improvement on 3 PD patients who underwent bilateral pallidal stimulation. Chronic high frequency stimulation of the Gpi has been shown to improve off symptoms, dyskinesias and motor fluctuations.

STN stimulation is a remarkable tool and one of the most effective therapies for treating all symptoms of PD, particularly off-period akinesia and rigidity. The lack of permanent side effects and the possibility of performing bilateral implantation in one session, without significant permanent neuropsychologic side effects are the most important arguments in support of this method. Limousin et al. evaluated 24 PD patients who received bilateral STN stimulation for 12 months and found that off-medication, UPDRS, and motor scores improved 60% ($p < 0.001$), while levodopa dosage was decreased by 50%. Krack et al. followed 15 PD patients with tremor who received STN stimulation and reported a reduction of 80% in UPDRS tremor score and 65% reduction in rigidity 1 to 12 months following surgery. Transient side effects included postoperative confusion, lower limb thrombophlebitis, seizures and stimulation-induced dyskinesias that resolved with adjustment of stimulation parameters.

We think that the advantages of DBS in front of ablative procedures are the reversibility, particularly of side effects in case of misplacement of the electrode, the adaptability of the parameters to fit the patient's clinical status and the possibility of performing a bilateral stimulation, however, the number of patients followed in this paper is too small to draw any definitive conclusion about the relative merits of the two procedures. Larger, randomized, blinded trials are required.

[7] COMPARISON OF ANATOMIC AND NEUROPHYSIOLOGICAL METHODS FOR SUBTHALAMIC NUCLEUS TARGETING. NEUROSURGERY 2000; 47: 282-294.

Information

Clinical studies have shown the efficacy of chronic subthalamic nucleus (STN) stimulation in alleviating all cardinal motor manifestations of PD including tremor, rigidity, bradykinesia, on/off fluctuations and dyskinesia. Given that the size of the STN has been estimated at 7x9x5mm, it is imperative that the anatomic localization of this relatively small target be as accurate as possible to minimize the numbers of microelectrode recording trajectories. The authors reviewed the various anatomic targeting methods and compared them with the final physiological target in 15 patients who underwent simultaneous bilateral STN implantation of deep brain stimulation (DBS). The coordinates of our localizing techniques were analyzed for 30 STN targets. The final target, determined by single cell microelectrode recording, were compared with the following:

- a) Target selected on coronal magnetic resonance images
- b) Stereotactic base atlas using the anterior and posterior commissures as landmarks.
- c) Using a predetermined formula which estimates the position of the STN from an atlas.
- d) A composite target based method.

For the authors, all anatomic targeting methods provides accurate STN localization, but a combination of the three methods offers the best correlation with the final physiological target.

Analysis

The STN is nowadays considered one of the most effective targets for DBS in advanced PD. This is a very good article that reviews targeting methods for placement of deep brain stimulators which leads into the STN, and compares these techniques with the physiological confirmation in the form of microelectrode recording. Since this nucleus is quite small (7x9x5mm), it is very important that the localization be as accurate as possible to avoid the stimulation of adjacent structures. All anatomic methods yielded targets that were statistically different ($p < 0.001$), from the final physiological targets. The average distance error between the final physiological targets and the magnetic resonance imaging derived targets was 2.6+/-1.3mm; for the atlas based method 1.7+/-1.1mm; for the indirect midcommissural method 1.5+/-0.8mm and for the composite method 1.3+/-1.1mm. The only anatomic technique that was statistically significantly more accurate than MRI-based targeting was the composite method. The least accurate anatomic method was direct MRI based targeting. Thus, although the use of direct MRI targeting can be readily visualized, the current technical limitations prevent it from being the most accurate. We agree with the authors than a combination of these three methods offers the best correlation with the final physiological target.

[8] ACUTE EFFECTS OF BILATERAL SUBTHALAMIC NUCLEUS STIMULATION ON CLINICAL AND KINEMATIC PARAMETERS IN PARKINSON'S DISEASE. MOVEMENTS DISORDERS 2001;16: 651-655.

Information

Bilateral high frequency stimulation of the subthalamic nucleus has been shown to improve the cardinal motor symptoms of advanced PD, and reduce the requirement for medication. After implantation with subthalamic stimulators, nine patients with advanced PD were studied on the task of tracing out, as accurately as possible, the four corners of a square with the dominant hand. The task was performed in four treatment conditions: on stimulation-off medication; off stimulation-off medication; off stimulation-on medication and on stimulation-on medication. Movement times and peak velocities improved significantly only in the on stimulation-on medication condition, compared to off stimulation-off medication. The improvement in clinical parameters with stimulation only was a borderline significance, while consistent and significant clinical improvement was only obtained with addition of medication (on medication-on stimulation).

Analysis

The authors give their experience in one study designed to investigate the acute effects of medication and subthalamic nucleus stimulation. Nine patients with advanced PD after implantation with subthalamic stimulators were studied. The order of the treatment conditions was always the same: on stimulation-off medication (on-off), off stimulation-off medication (off-off), off stimulation-on medication (off-on) and on stimulation-on medication (on-on). The instructions were to trace out, using the plastic rod, the four corners of the square in a clockwise direction, as precisely as possible, pausing momentarily at each corner, the patients performed the entire motor task in each of four condition in the same morning.

Compared to the off-off condition, subthalamic nucleus stimulations produced a 28% reduction in UPDRS scores ($p=0.008$); medication produced a 77% reduction ($p=0.001$); and stimulation plus medication an 88% reduction ($p<0.001$).

Clinically, the authors found that off medication-on stimulation UPDRS deteriorated by 28% when the stimulator was turned off; and that off medication and off stimulation UPDRS scores improved by 77% after medication. This indicates that the acute clinical effect of stimulation alone is smaller than acute effect of medication alone.

In conclusion, the authors give evidence that subthalamic stimulations increase the effect of medication in the treatment of PD and suggests that the combination of medication and surgery is superior than either treatment alone.

[9] OUTCOMES AND COMPLICATION OF FETAL TISSUE TRANSPLANTATION IN PARKINSON'S DISEASE
STEREOTACTIC FUNCT NEUROSURG 1999; 72: 219-224.

Information

This study was undertaken to investigate the outcome, complication rates and risk factors of stereotactic intrastriatal neurotransplantation for PD. Sixty patients were stabilised on medications and received MRI and at least two neurological evaluation in both "on" and "off" conditions during a minimum of 6 months presurgery evaluation period. The patient's function was assessed according to the CAPIT protocol, using the UPDRS, in videotaped evaluation sessions. In the stereotactic neurotransplantation procedure, four grafts were implanted through a superior entrance point into the postcommissural putamen of each hemisphere. Overall the 45 neurotransplantation patients with a 12 month follow up demonstrated significant improvement of 44.5% in UPDRS scores (from 54.8 +/- 2.5 preoperatively to 30.4 +/- 2.4, twelve months postoperatively). Three patients (5%), discontinued medication altogether after transplantation ; 3 patients (5%) have not exhibited any improvement. L-Dopa dosages for all 60 patients declined by 17.8% . Nine patients experienced adverse effects after the transplantation. Four patients exhibited frontal lobe symptoms including confusion, disorientation and inappropriate behavior. These symptoms disappeared by 12 weeks postoperatively in 3 patients. An additional patient exhibited increased dyskinesia and could not be alleviated by adjustment of the medical regimen but was effectively resolved with pallidotomy. Three patients developed hematomas; two of these requiring surgical removal. An asymptomatic cyst in one patient was only revealed 22 months after transplantation. One patient suffered postoperative seizures which were treated with phenytoin for 4 months, after which medication was discontinued with no further episodes.

Analysis

Since 1988, neurotransplantation with embryonic dopamine cells has been tried as a treatment for patients with advanced PD. Although transplant methods have differed substantially among centers, most reports have found some efficacy to tissue implants made into caudate and putamen. Reduction of L-Dopa dose requirements is frequently reported. The mesencephalic tissue must be from early in embryonic development, typically 7 to 8 weeks after conception. Bilateral transplantation into putamen can be done safely during a single operation. Unilateral transplantation leads to asymmetric transplant effects. Although the clinical benefit in individual patients has made drug elimination possible, there is substantial variability in outcome. The present study has analyzed the incidence of complications in 60 patients who underwent neurotransplantation for PD. Fifteen transplant patients are not included in the 12 month follow-up because they either withdrew from the protocol or are not yet 12 months postoperative. Complications were attributed to: patient selection, transplanted tissue, neurosurgical procedure or postoperative care. Adverse outcomes occurred in 9 patients. All but one complication (dyskinesia), are related to the stereotactic neurosurgical procedure and not to neurotransplantation. There was no explanation why this patient developed dyskinesia. The paper showed a

significant improvement in UPDRS scores 12 months after transplantation (44.5%), but the evaluators were not blinded, a factor that led to uncertainty regarding the efficacy of the procedure.

[10] TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE PARKINSON'S DISEASE
N ENGL J MED 2001 344: 710-719

Information

The authors randomly assigned 40 patients who were 34 to 75 years of age and had severe PD (mean duration 14 years), to receive a transplant of nerve cells or undergo sham surgery; all were to be followed in a double-blind manner for one year. In the transplant recipients, cultured mesencephalic tissue from four embryos was implanted into the putamen bilaterally. In the patients who underwent sham surgery, holes were drilled in the skull but the dura was not penetrated. The primary outcome was a subjective global rating of the change in the severity of disease scored on a scale of -3.0 to 3.0 at one year with negative scores indicating a worsening of symptoms and positive scores an improvement. Among younger patients (<60 years), tests of Parkinson's disease revealed significant improvement in the transplantation group as compared with the sham surgery group when patients were tested in the morning before receiving medication ($p=0.01$ for UPDRS; $p=0.006$ for the Schwab and England scores). There was no significant improvement in older patients (>60 years), in the transplantation group.

Fibre outgrowth from the transplanted neurons was detected in 17 of the 20 patients in the transplantation group, as indicated by an increase in 18F-fluorodopa uptake on positron-emission tomography or post-mortem examination.

After improvement in the first year, dystonia and dyskinesia recurred in 15% of the patients who received transplants, even after reduction or discontinuation of the dose of levodopa.

Analysis

The authors published the results of a trial of embryonic cell transplantation for patients with severe PD. Forty patients were randomly assigned to receive either fetal tissue transplantation or sham surgery. A total of 39 patients completed the study. One patient in the transplantation group died in an automobile accident seven months after surgery.

After 1 year, the global rating scale scores, failed to demonstrate significant differences between the transplanted-treated and the sham-treated groups. In an evaluation of secondary end points, it was observed that younger patients (<60 years), demonstrated significant improvement when evaluated using the UPDRS ($p=0.001$) and the Schwab and England Disability Scores ($p=0.006$). There was no significant improvement among older patients despite PET revealed an increase in dopamine activity in more than 66% of the treated patients.

Autopsy results in two older patients (66 and 71 years old), confirmed the growth of the transplants in the putamen.

A very important point is that 15% of the patients who received fetal transplants developed dystonia and dyskinesia that persists even after reduction or elimination of dopaminergic agonist therapy. The authors' explanation for these findings was the excessive dopamine production by the transplants cells, and the simplest answer to the problem could involve using less tissue in the future. We do not agree with the authors because many transplantation efforts have been made using greater amounts of tissue and those patients have not demonstrated this severe postoperative dyskinesia. Most of the reported dyskinesia was observed shortly after surgery, when some tissue was probably dying and releasing excessive amounts of dopamine. For us, these findings re-emphasise the experimental nature of these procedures and indicate that further observation and analysis of patients who have undergone transplantation are warranted.

Synthesis

Neurosurgical procedures are very important for the treatment of Parkinson's Disease. Thalamotomy and thalamic stimulation appears to provide comparative efficacy to reduce contralateral tremor (principally essential tremor). Advantages of thalamic DBS over thalamotomy adjustability of stimulation parameters (to avoid collateral effects related to stimulation) and reversibility of the procedure (the electrode can be explained). Disadvantages of chronic stimulation include infections, hardware malfunction and battery replacement. Bilateral thalamotomies are usually avoided.

Pallidotomy is an effective treatment for patients with PD. The procedure improves motor performance as well as total activities of daily living during the off period and drug induced dyskinesias during the on period. Bilateral pallidotomy reduced dyskinesia, but is associated with an increased risk of complication including cognitive and bulbar symptoms, especially dysarthria and swallowing difficulties.

Pallidal and Subthalamic stimulation produced good improvement in rigidity, dyskinesia and tremor; but there was greater improvement in akinesia score in the STN stimulation group. The surgical side effects are rare and markedly less than in lesional procedures. Stimulation dependent side effects usually can be outweighed by parameter adjustments.

It has been demonstrated that transplants of embryonic dopamine neurons survive in the putamen of patients with PD and provide benefit in some young patients. However, this procedure has been tempered by the emergence of dyskinesia and dystonia in some patients with transplants even without medication. This adverse effect requires close study to assess its impact, understand its physiological basis, and determine whether it can be avoided in the future.

We think that is very important to select the right surgery for the right patient. A teamwork between neurologist, neurosurgeons, psychologist and physical therapists is strongly recommended and a critical documentation of the results,

side effects and complications is required to optimize the therapy for future patients with PD.

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