Long-term Evaluation of Bilateral Fetal Nigral Transplantation in Parkinson Disease

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Background: Parkinson disease (PD) is associated with a progressive loss of nigrostriatal dopamine neurons. Medication therapy provides adequate control of symptoms for several years, but long-term treatment is complicated by progressive disability and the development of motor fluctuations and dyskinesias. In animal models of PD, fetal nigral transplants have been shown to survive grafting into the striatum, provide extensive striatal reinnervation, and improve motor function. In patients with PD, cell survival and clinical benefit have been observed following fetal nigral grafting, but results have been inconsistent.

Objective: To evaluate the safety and efficacy of bilateral fetal nigral transplantation into the postcommisural putamen in patients with advanced PD complicated by motor fluctuations and dyskinesias.

Patients and Methods: Six patients with advanced PD underwent bilateral fetal nigral transplantation. Each patient received solid grafts derived from donors aged 6 1/2 to 9 weeks after conception stereotactically implanted into the postcommissural putamen using 3 to 4 donors per side. Cyclosporine was administered for approximately 6 months to provide immune suppression. Clinical evaluations included the Unified Parkinson's Disease Rating Scale (UPDRS), Schwab-England Activities of Daily Living Scale, and timed tests of motor function conducted during both the “off” and “on” states at baseline and at 1, 3, 6, 9, 12, 18, and 24 months following transplantation. Percentage of time off and percentage of time on with and without dyskinesia were recorded at half-hour intervals using home diaries during the week prior to each evaluation. 18F-fluorodopa positron emission tomographic scans were performed at baseline, and at 6 months and 1 year following transplantation.

Results: Patients have been followed up for a mean ± SD of 20.5 ± 5.5 months. Complications related to surgery were mild and transient. Activities of daily living, motor, and total (activities of daily living plus motor) UPDRS scores during the off state improved significantly (P<.05, Wilcoxon signed rank test) at final visit in comparison with baseline. Mean total UPDRS off score improved 32%, and each patient experienced at least a 19% improvement. Mean percentage of time on without dyskinesia during the waking day improved from 22% to 60% (P<.05). Mean putamenal fluorodopa uptake on positron emission tomography increased significantly at 6 and 12 months in comparison with baseline (P<.001, 2-tailed t test). This increase correlated with clinical improvement. Two patients died 18 months after transplantation from causes unrelated to the surgical procedure. In both cases, histopathological examination showed robust survival of tyrosine hydroxylase immunoreactive cells and abundant reinnervation of the postcommissural putamen.

Conclusions: Fetal nigral tissue can be transplanted into the postcommissural putamen bilaterally in patients with advanced PD safely and with little morbidity. In this open-label pilot study we observed consistent long-term clinical benefit and increased fluorodopa uptake on positron emission tomography. Clinical improvement appears to be related to the survival and function of transplanted fetal tissue.

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PATIENTS AND METHODS

Patients with advanced PD who could not be further improved by adjustments in medical therapy underwent bilateral fetal nigral transplantation into the postcommisural putamen (PCP) according to a previously described protocol.23 All patients had at least 2 of 3 cardinal features of PD (resting tremor, rigidity, or bradykinesia) and a good response to levodopa therapy as defined by the Core Assessment Program for Intracerebral Transplantations (CAPIT).22 Each exhibited relatively predictable motor fluctuations and were Hoehn-Yahr stage III or better while on. All patients had been receiving a stable dose of levodopa-carbidopa for a minimum of 3 months prior to study entry and all provided written informed consent.

Patients were screened for human immunodeficiency virus types 1 and 2, human T-lymphotropic virus, hepatitis A, B, and C, cytomegalovirus, toxoplasma, syphilis, and herpes simplex. Those with serologic evidence of infection with human immunodeficiency virus, human T-lymphotropic virus, hepatitis, or syphilis were excluded. Patients who had negative findings for cytomegalovirus or toxoplasma were also excluded to eliminate the risk of transplanting these infectious agents into a naive recipient.

Fetal tissue was obtained from women undergoing elective abortions in accordance with federal and state laws, National Institutes of Health guidelines, the Uniform Anatomical Gift Act as adapted by the State of Florida, and applicable university and hospital internal review board guidelines.23 Maternal donors were screened for the transmittable infectious agents listed above and fetal tissue was cultured for bacteria and yeast. Donor age was assessed according to the atlas of O'Rahilly and Muller24 for donors younger than 8 weeks after conception and by a combination of foot length, heel length, and greatest length for older donors.25,26 Mesencephalons from donor embryos aged 6 1/2 to 9 weeks after conception29,30 were dissected and stored in “hibernation medium” at 8°C for up to 2 days.31 Tissue was further dissected into 3/4 mm3 pieces in chilled Hanks balanced salt solution immediately before transplantation.23,30,31

Solid grafts of mesencephalon were implanted bilaterally into the PCP in 2 staged procedures separated by approximately 4 weeks. Tissue from 3 to 4 embryos was implanted per side. At the time of surgery, patients were placed in a Cosman-Roberts-Wells stereotactic frame (Radionics, Burlington, Mass) using local anesthesia and the putamen was visualized on high-field strength magnetic resonance imaging (1.5 T) using a fast spin-echo sequence (repetition time/echo time, 3200 milliseconds/17; matrix, 256 × 256; field of view, 30 cm).32 The initial target site (“zero point”) was identified as the ventrolateral putamen at the level of the genu of the internal capsule. Patients were then taken to the operating room and anesthetized using fentanyl and propofol, with laryngeal mask airway protection.32 A burr hole was placed at the coronal suture and a putamen-shaped grid array with holes at 3-mm intervals was placed onto the stereotactic frame.33,34 The transplant needle was then directed to the magnetic resonance imaging-determined zero point of the putamen. Subsequent needle placements were made by manipulating the grid array on the stereotactic frame to use the same cortical entry point. Tissue from half of a mesencephalon (ie, 1 substantia nigra) was deposited into each needle tract. Six to 8 needle tracts were used per side and 4 tissue deposits were placed into each tract so that graft deposits were separated by no more than 5 mm in all 3 dimensions. Broad-spectrum antibiotics were provided perioperatively and treatment with them discontinued if tissue cultures were negative. All patients underwent postoperative magnetic resonance imaging.

Immunosuppression was employed using cyclosporine. Cyclosporine was initiated at a dose of 6 mg/kg per day 2 weeks before the first transplantation procedure, reduced to 2 mg/kg per day 2 weeks after the second procedure, and discontinued after 6 months. Serum urea nitrogen and creatinine levels were monitored biweekly and the cyclosporine dose was lowered or discontinued as deemed clinically appropriate. Following surgery, antiparkinsonian medications were reinstituted at preoperative doses and we tried to maintain these doses throughout the study.

Clinical evaluations were performed at baseline and at 1, 3, 6, 9, 12, 18, and 24 months following transplantation. Each evaluation included Unified Parkinson's Disease Rating Scale (UPDRS) and Schwab-England assessments. In addition, the time (in seconds) required for the patient to perform 20 cycles of pronation/supination with each arm was determined. These evaluations were conducted as per the Core Assessment Program for Intracerebral Transplantation22 protocol in both the practically defined off state (after medication was withheld overnight for 12 hours) and the on state (peak response after administration of the patient's usual morning medication dose). Percentage of time off and percentage of time on with and without dyskinesia were recorded at half-hour intervals using home diaries during the week before each evaluation.

18F-fluorodopa PET scans were performed at baseline, and at 6 months and 1 year following transplantation.35 Scans were analyzed to determine the striatal FD uptake rate constant (Ki) using the method of Patlak and Blasberg36 as previously described.37

Statistical analysis comparing clinical scores at final evaluation to baseline were performed using a Wilcoxon signed rank test. Fluorodopa PET analysis was performed using a 2-tailed t test.

because (1) the neuronal loss is relatively site and type specific (nigrostriatal DA neurons), (2) the target area for implantation (striatum) is well defined and limited in size, (3) downstream mechanisms are relatively intact as evidenced by a continued response to DA replacement therapy, and (4) DA neurons normally provide tonic stimulation of target receptors and appear to serve a modulatory function. In animal models of PD, fetal nigral dopaminergic transplants have been shown to survive grafting into the striatum, provide extensive striatal reinnervation, form synaptic connections, exhibit relatively normal electrical firing patterns, and improve motor function.38-41 In those with PD, clinical benefit has been observed following fetal nigral grafting, but results have been inconsistent.12-13 This variability may be due to differences in the transplant variables and the methods of evaluation used.22 We designed a protocol aimed at maximizing the likelihood of graft survival and previously re-
ported 6-month results for the first 4 patients who had undergone fetal mesencephalic transplantation according to this protocol. They experienced consistent clinical benefit and increased fluorodopa (FD) uptake on positron emission tomography (PET). We now report the longer-term results of transplantation for the first 6 patients (including the original 4) to undergo transplantation according to our protocol.

**RESULTS**

Six patients underwent transplantation according to this protocol. These were consecutively operated on cases and compose the entire group of patients with PD who underwent open-label transplantation at our institution. They have been followed up over a 24-month observation period. Because 2 patients died approximately 18 months after transplantation, final clinical evaluations ranged from 12 to 24 months (mean ± SD, 20.5 ± 5.5 months) following surgery. Patient demographics and time of last evaluation are presented in Table 1. Patients participating in this study had a mean ± SD disease onset at 37.3 ± 7.9 years and a disease duration of 18.2 ± 7.6 years.

Surgeries were well tolerated and patients were discharged from the hospital within 1 to 2 days. Patient 1 experienced confusion, hallucinations, and paranoid ideation 1 month following surgery. He had found to have a urinary tract infection and was thought to have nonconvulsive seizures although an interictal electroencephalogram was normal. He improved with a reduction of levodopa dose, treatment of his urinary tract infection, and introduction of carbamazepine. He had no further episodes of confusion. Patient 3 had an asymptomatic cortical hemorrhage on routine postoperative magnetic resonance imaging. Patient 6 experienced vomiting and dehydration with a rise in serum urea nitrogen and creatinine levels to 21.4 mmol/L and 221 µmol/L (2.5 mg/dL), respectively, 3 weeks after the first operation. Use of cyclosporine was discontinued and clinical symptoms and laboratory abnormalities resolved. The second operation was delayed for 1 month and performed without reinstitution of cyclosporine. Antiparkinsonian medications for each patient at baseline and at last evaluation are shown in Table 2. For the group, the mean daily levodopa dose was 16% lower at last evaluation compared with baseline but not significantly changed (Table 3).

Two patients died of causes unrelated to the surgical procedure. Patient 1 died 18 months after transplantation as a result of a pulmonary embolus that occurred 6 months following ankle fusion surgery for posttraumatic degenerative arthritis. Patient 5 died abruptly 18 months following transplantation surgery. This oc-

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**Table 1. Patient Demographics and Time to Last Evaluation**

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Disease Duration, y</th>
<th>Last Evaluation, mo</th>
<th>Death, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/59</td>
<td>8</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>2/M/39</td>
<td>12</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>3/F/61</td>
<td>22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>4/M/50</td>
<td>15</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>5/F/61</td>
<td>27</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>6/M/63</td>
<td>25</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>55.5 (9.3)*</td>
<td>18.2 (7.6)*</td>
<td>20.5 (5.5)*</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean (SD).

**Table 2. Daily Antiparkinsonian Medication Doses at Baseline and Last Evaluation**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Medication Baseline, mg</th>
<th>Last Evaluation, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Levodopa-carbidopa CR</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Levodopa-carbidopa</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>Levodopa-carbidopa</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Pergolide</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Trihexyphenidyl</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Levodopa-carbidopa</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>Pergolide</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Levodopa-carbidopa CR</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>Levodopa-carbidopa</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>Pergolide</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Levodopa-carbidopa</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>Pergolide</td>
<td>1.25</td>
</tr>
<tr>
<td>6</td>
<td>Levodopa-carbidopa CR</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>Levodopa-carbidopa</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Amantadine</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>5</td>
</tr>
</tbody>
</table>

*Ellipses indicate that the patient was no longer taking that particular medication.

**Table 3. Levodopa Dose and Clinical Scores at Baseline and Last Evaluation**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Last Evaluation</th>
<th>P</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levadopa dose, mg/d</td>
<td>854.2 (160.4)</td>
<td>716.7 (140.0)</td>
<td>.16</td>
</tr>
<tr>
<td>UPDRS “on”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL</td>
<td>7.9 (0.9)</td>
<td>7.5 (2.6)</td>
<td>.89</td>
</tr>
<tr>
<td>Motor</td>
<td>12.7 (2.4)</td>
<td>14.1 (3.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total</td>
<td>19.9 (3.1)</td>
<td>21.6 (6.0)</td>
<td>.89</td>
</tr>
<tr>
<td>Pronation/supination “on”</td>
<td>11.7 (0.5)</td>
<td>11.9 (1.7)</td>
<td>.80</td>
</tr>
<tr>
<td>UPDRS “off”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL</td>
<td>32.1 (2.9)</td>
<td>21.0 (3.2)</td>
<td>.028†</td>
</tr>
<tr>
<td>Motor</td>
<td>50.8 (7.2)</td>
<td>35.4 (6.2)</td>
<td>.04†</td>
</tr>
<tr>
<td>Total</td>
<td>82.9 (6.6)</td>
<td>56.4 (9.0)</td>
<td>.028†</td>
</tr>
<tr>
<td>Pronation/supination off‡</td>
<td>26.2 (6.9)</td>
<td>17.5 (2.8)</td>
<td>.008†</td>
</tr>
<tr>
<td>Schwab-England on</td>
<td>88.3 (1.1)</td>
<td>85.8 (2.4)</td>
<td>.42</td>
</tr>
<tr>
<td>Schwab-England off</td>
<td>56.7 (4.8)</td>
<td>70.8 (4.9)</td>
<td>.12</td>
</tr>
<tr>
<td>Off time</td>
<td>34.8 (5.1)</td>
<td>19.7 (5.1)</td>
<td>.12</td>
</tr>
<tr>
<td>% time of dyskinesia</td>
<td>43.5 (11.2)</td>
<td>20.5 (8.6)</td>
<td>.17</td>
</tr>
<tr>
<td>% time on without dyskinesia</td>
<td>21.8 (7.1)</td>
<td>59.8 (12.5)</td>
<td>.046†</td>
</tr>
</tbody>
</table>

*UPDRS indicates Unified Parkinson’s Disease Rating Scale; ADL, activities of daily living; and ellipses, not applicable. Values are mean (SE) unless otherwise indicated.

†P<.05.
‡ Mean seconds to perform 20 cycles of pronation/supination in each arm.
curred shortly after eating; she may have aspirated and suffered a cardiac arrhythmia.38

Clinical scores at baseline and last evaluation are presented in Table 3. Activities of daily living (ADL), motor, and total (ADL plus motor) UPDRS scores during the off state improved significantly \((P < .05)\). Mean total UPDRS off score improved by 32%, and each patient experienced at least a 19% improvement (range, 19.7%-56.9%). Pronation/supination speed during the off state improved by 33% \((P = .01)\). Mean percentage of the waking day in the on state without dyskinesia improved from 22% to 60% \((P < .05)\). Correspondingly, off time decreased by 43% \((P = .12)\) and percentage of time on with dyskinesia decreased by 53% \((P = .17)\). Schwab-England off scores improved 25% \((P = .12)\). Mean UPDRS, Schwab-England, and pronation/supination scores during the on state were unchanged from baseline. Improvements over time in total UPDRS off scores and percentage of time on without dyskinesia are depicted in Figure 1 and Figure 2. In general, improvement was observed at 1 month (2 months after initial surgery), and increased through 3 to 6 months. In the 4 patients who completed 24 months of evaluation, improvement in UPDRS off scores persisted throughout the observation period (Figure 1, B). There was a slight trend for partial loss of benefit in percentage of time on without dyskinesia at 12 to 24 months, but values remained improved compared with baseline (Figure 2, B).

The results of FD PET at baseline and 6 and 12 months are shown in Table 4. Significant and progressive increases in mean putamenal \(Ki\) were observed at 6 and 12 months in comparison with baseline \((P < .001\) and \(P < .0001\), 2-tailed \(t\) test). Mean putamenal \(Ki\) increased by 48% at 6 months and 61% at 12 months. At 12 months the mean putamenal \(Ki\) for the group was approximately 55% of the value in normal individuals.35,39 \(Ki\) was increased in 11 of the 12 implanted putamina and each patient exhibited at least a 42% increase on one side. The increase in FD uptake correlated with improvements in UPDRS total off scores \((r = 0.80; P = .005)\), percentage of time on with dyskinesia \((r = 0.74; P = .02)\), percentage of time off \((r = 0.73, P = .03)\), and percentage of time on without dyskinesia \((r = 0.59; P = .03)\). Patient 6 demonstrated a 118% increase in left putamenal \(Ki\) at 1 year, despite having undergone transplantation on that side following withdrawal of cyclosporine. Mean caudate \(Ki\)'s for the group were unchanged.

Autopsy results from the 2 patients who died have been reported elsewhere.37,38,41 In brief, histopathological examination revealed abundant DA cell survival and robust reinnervation of the PCP in both cases. Tyrosine hydroxylase (TH) immunoreactive cell counts ranged from 81 905 to 135 673 in the implanted putamina.

**COMMENT**

We observed consistent clinical benefit after a mean follow-up of 20.5 months in 6 patients with PD who underwent fetal nigral transplantation according to our pro-
Table 4. 18F-Fluorodopa Uptake*

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 12)</th>
<th>6 mo (n = 10)</th>
<th>12 mo (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen, mL·min⁻¹·cc⁻¹</td>
<td>0.0069 (0.0005)</td>
<td>0.0102 (0.0005)</td>
<td>0.0111 (0.0007)</td>
</tr>
<tr>
<td>Caudate, mL·min⁻¹·cc⁻¹</td>
<td>0.0125 (0.0009)</td>
<td>0.01359 (0.0014)</td>
<td>0.0126 (0.0008)</td>
</tr>
</tbody>
</table>

*Comparisons are to baseline, using paired t test. Values are mean (SE).

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6 to 12 weeks after unilateral grafting that plateaued at about 4 to 5 months.

Putamenal FD uptake on PET was significantly increased at 6 (48%) and 12 months (61%). These figures likely underestimate the magnitude of improvement in the transplanted region (PCP) as PET measurements were derived from the entire putamen. At 12 months, mean ± SE putamenal Ki was 0.0111 ± 0.0007, or approximately 55% of the value in normal individuals. The increase in putamenal FD uptake following transplantation correlated with clinical improvement. This finding is consistent with an earlier report indicating that FD uptake on PET correlates with clinical improvement.

The findings of increased FD uptake on PET and robust survival of DA neurons at autopsy suggest that the clinical benefits observed were attributable to the survival and function of transplanted cells. A trophic effect is unlikely as no host-derived sprouting was identified and lesion-induced sprouting in the putamen has not been reported. We are not able to exclude the possibility of a placebo effect as this was an open-label study. However, the persistence of clinical improvement through 24 months due solely to a placebo effect seems unlikely. We are also not able to exclude the possibility that clinical benefit was related to cyclosporine therapy, through either a symptomatic or antiapoptotic mechanism. However, cyclosporine was administered for only 6 months after transplantation and improvement in UPDRS off scores persisted through the 24-month observation period. It seems unlikely that cyclosporine could provide sustained clinical benefit following its withdrawal. Furthermore, comparable clinical benefits were observed in the patient who was withdrawn from cyclosporine. We are now conducting a prospective, randomized, blinded, controlled study to better assess the magnitude of efficacy directly attributable to the surgical procedure.

Two patients in this series died 18 months after surgery. Patient 1 suffered a pulmonary embolus that may have been related to ankle fusion surgery. His mobility had improved sufficiently following fetal nigral transplantation to warrant such surgery to ameliorate symptoms related to long-standing posttraumatic arthritis. Patient 5 may have died from aspiration, perhaps suggesting that fetal nigral transplantation did not improve her swallowing mechanisms sufficiently to avoid aspiration. Although neither patient’s death was directly attributable to transplantation surgery, an accurate assessment of long-term adverse events remains to be determined in larger, controlled studies.

Although our patients experienced considerable improvement in FD uptake on PET and robust cell survival was identified on autopsy in 2 cases, they continued to require levodopa and had residual clinical disability, motor fluctuations, and dyskinesia. Some strategies to improve outcome following transplantation are presented below.

**INCREASE THE NUMBER AND FUNCTION OF SURVIVING TRANPLANTED CELLS**

More than 80,000 neurons per PCP survived transplantation in our autopsy cases. Normally, about 60,000 TH immunoreactive neurons project to each putamen. Thus, it appears that a supranormal number of DA neurons survived transplantation using our protocol. However, not all TH-staining neurons necessarily project to the striatum or are functioning DA neurons. DA neurons originating in the ventral tegmental area do not send processes to the striatum. Greater clinical benefit might be achieved by transplanting a greater number of donor nigral or by improving cell survival. We transplanted 3 to 4 fetal mesencephalons per side in this study and others are now transplanting 7 to 8. In addition, trophic factors and trophic factor–secreting cells have been shown to augment the viability of transplanted cells and enhance neuritic extension. Preclinical evidence also suggests that treatment with antioxidants or lasseroids increases cell viability after grafting. These approaches might increase survival and function of transplanted cells in patients with PD and improve clinical benefit.

**INCREASE THE AREA OF REINNERVATION DERIVED FROM AN INDIVIDUAL GRAFT**

Based on our animal studies, we estimated that graft deposits developed concentric neuritic outgrowth with a radius of approximately 2.5 mm. Accordingly, we placed grafts at 5-mm intervals in all 3 dimensions throughout the target region. Autopsy studies indicated that this approach provided confluent reinnervation between deposits and the territory of reinnervation surrounding each graft deposit was between 2.5 and 7 mm. This suggests that graft deposits can be spaced at greater intervals than were used herein, thereby permitting a greater territory to be reinnervated with the same amount of implanted tissue. New approaches using trophic factors or spermatids are being investigated to test their ability to increase neuritic outgrowth, expand the territory of influence of grafted cells, and improve clinical outcome.

**PROLONGED USE OF IMMUNOSUPPRESSION**

Whether immunosuppression is required for graft survival and clinical benefit remains unclear. Fetal allografts in rodents and nonhuman primates can survive and provide behavioral effects for extended periods without immunosuppression. Furthermore, there have been reports of clinical benefit in patients who received fetal grafts without immunosuppression. However, cyclosporine improves survival of xenografts in rodent models. In addition, there are examples of allograft rejection in immunologically disparate rodents, which may be particularly relevant in our protocol in that multiple allografts were used. Our experience indicates that immunosuppression beyond 6 months posttransplantation may not be necessary for persistent graft survival and continued clinical benefit. In our series, FD uptake on PET continued to increase from 6 to 12 months despite discontinuation of cyclosporine at 6 months. Additionally, DA cell survival was reported 7 months posttransplantation in a patient who did not receive immunosuppression. It is possible that immunosuppression is not necessary for clinical benefit after transplantation. However, we have recently demonstrated the presence of immune markers for microglia, macrophages, and B and T cells within...
grafted regions 18 months posttransplantation. The significance of these cells is unknown but their presence raises the possibility that more sustained or more effective immunosuppression might improve cell survival and long-term outcome.

**ELIMINATE LEVODOPA**

The use of levodopa might compromise clinical benefit from transplantation as levodopa is toxic to cultured DA neurons and has been reported to reduce the maturation, growth, and function of transplanted DA cells. Our patients continued to experience clinical benefit despite levodopa administration and autopsy studies demonstrated abundant survival of transplanted DA neurons at 18 months. These observations indicate that levodopa does not preclude cell survival and long-term clinical benefit in patients with PD following transplantation. However, it is possible that our patients would have had greater cell survival and enhanced clinical benefit if levodopa had been discontinued.

**USE ALTERNATE TARGET AREAS**

We chose to target the PCP for implantation because it is the most affected region in PD and because it is anatomically linked to motor circuitry. However, PD is also associated with degeneration of mesencephalic DA neurons that project to other cortical and brainstem regions and it is possible that patients might experience additional benefits with implantation into alternate sites such as the caudate nucleus, substantia nigra pars compacta, or nucleus accumbens. In rodent and monkey models, transplantation is associated with site-specific behavioral effects. In 6-hydroxydopamine-lesioned rodents, grafting into the dorsal striatum improves rotational asymmetry whereas grafting into the ventrolateral striatum ameliorates sensorimotor attentional deficits. In monkeys, grafts placed into the putamen improve skilled motor tasks and reduce contralateral neglect whereas grafts placed into the caudate nucleus improve rotational asymmetry. Transplantation into the caudate nucleus may provide specific benefits for patients with PD. In nonhuman primates, hemiparkinsonism can be induced by injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine into the caudate nucleus and improvement in motor function has been reported in both monkeys and patients with PD after transplantation solely into the caudate nucleus.

Positron emission tomography and autopsy studies suggest that this benefit is related to the survival and function of transplanted DA neurons. In light of these encouraging findings, we are now conducting a larger, controlled, blinded study to better evaluate the long-term safety and efficacy of fetal nigral transplantation in patients with PD.

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**REFERENCES**


