

Case Report/Case Series

Long-term Clinical Outcome of Fetal Cell Transplantation for Parkinson Disease

Two Case Reports

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IMPORTANCE Recent advances in stem cell technologies have rekindled an interest in the use of cell replacement strategies for patients with Parkinson disease. This study reports the very long-term clinical outcomes of fetal cell transplantation in 2 patients with Parkinson disease. Such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation.

OBSERVATIONS Two patients received intrastriatal grafts of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts, as restorative treatment for their Parkinson disease. To evaluate the very long-term efficacy of the grafts, clinical assessments were performed 18 and 15 years posttransplantation. Motor improvements gained gradually over the first postoperative years were sustained up to 18 years posttransplantation, while both patients have discontinued, and remained free of any, pharmacological dopaminergic therapy.

CONCLUSIONS AND RELEVANCE The results from these 2 cases indicate that dopaminergic cell transplantation can offer very long-term symptomatic relief in patients with Parkinson disease and provide proof-of-concept support for future clinical trials using fetal or stem cell therapies.

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Recent advances in stem cell technologies have rekindled an interest in the use of reparative strategies for patients with Parkinson disease (PD).¹ The ethical concerns related to using human fetal dopaminergic cells and the problems of securing a reliable supply of standardized cells can now be more easily addressed, thus allowing cell transplantation to be reconsidered as a potential treatment option for well-selected patients in a trial setting. Nevertheless, the overall strategy of using dopaminergic cell replacement as a treatment for PD remains the subject of ongoing critical evaluation.²

The purpose of this study was to report the very long-term outcome of 2 patients with PD who received human fetal ventral mesencephalic neural grafts and thus demonstrate the magnitude and duration of the therapeutic effect that can occur using a cell replacement strategy. Such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation.

Report of Cases

Methods

We describe 2 patients (patients 7 and 15 in the Lund series) who received intrastriatal transplantations of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts, as an experimental treatment for their PD.^{3,4} Throughout their disease course, both patients experienced excellent responses to levodopa treatment. However, both subsequently developed disabling “on-off” fluctuations with accompanying severe levodopa-induced dyskinesias (LIDs). The patients were clinically followed up at the National Hospital for Neurology and Neurosurgery, Queen Square, London, England. Transplantation was performed in Lund, Sweden. The grafts were placed bilaterally using the Rehncrona and Legradi transplantation instrument in a staged manner. A magnetic resonance imaging-guided stereotactic technique was used for targeting the putamen

Table 1. Patient Characteristics Prior to Transplantation and Grafting Procedure Details

	Patient 7	Patient 15
Sex/handedness	Male/right-handed	Male/right-handed
Age at onset, y/disease duration, y	39/10	42/12
Disease phenotype	Akinetic rigid	Akinetic rigid
Mean UPDRS part III score in "practically defined off"/best "on" conditions (range, 0-108) ^a	38/11	23/3.4
PD-related medication	Levodopa, 300 mg/d; pergolide, 1.5 mg/d; selegiline, 10 mg/d; amantadine, 300 mg/d	Levodopa, 900 mg/d; pergolide, 1.5 mg/d; amantadine, 200 mg/d; 2-3 apomorphine injections (5 mg/0.5 mL)/d
Date/location of transplantation/No. of trajectories	Apr 1993/left putamen/5; Sep 1994/right putamen/5	Nov 1996/left putamen + caudate/5 + 2; Nov 1996/right putamen + caudate/5 + 2
No. per side/age of donors, wk postconception (embryos)	5/6-8	4/6-9
Transplantation preparation	Fresh tissue; cell suspension	Fresh tissue; cell suspension
Immunosuppression	Cyclosporin, azathioprine, prednisolone (2 d before to 48 mo after grafting)	Cyclosporin, azathioprine, prednisolone (2 d before to 20 mo after grafting)

Abbreviations: amantadine, amantadine hydrochloride; apomorphine, apomorphine hydrochloride; pergolide, pergolide mesylate; PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale.

^a Following a levodopa challenge using a suprathreshold dose of oral levodopa.

(patient 7) and the putamen and caudate nucleus (patient 15), at the ages of 49 and 54 years and after disease durations of 10 and 12 years, respectively. The patients' characteristics prior to transplantation and grafting procedures are summarized in **Table 1**.

To evaluate the very long-term efficacy of the grafts, clinical assessments were performed 18 and 15 years posttransplantation for patients 7 and 15, respectively. Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) motor examination (part III) in the presence and absence of medication (neither patient was receiving dopaminergic replacement therapy) (**Table 2**). Dyskinesias and "on-off" fluctuations were assessed by UPDRS part IV. The Abnormal Involuntary Movement Scale was further used to evaluate the severity of dyskinesias. The test battery also included Activities of Daily Living-UPDRS part II, the PD Non-Motor Symptoms Questionnaire, PDQ-39 questionnaire, and a neuropsychological assessment (**Table 2**).

Preoperative and postoperative clinical scores from assessments performed in our institution were compared with current scorings (**Figure 1**). Representative positron emission tomography scan images comparing preoperative and postoperative striatal 6-L-fluorodopa F 18 (¹⁸F-Dopa) uptake have been obtained from archival data (**Figure 2**).⁶

Both patients had Sanger and/or next-generation sequencing of the coding exons of all known PD genes including Parkin, *PINK-1*, and *DJ-1* as well as multiplex ligation-dependent probe amplification analysis to exclude presence of the G2019S *LRKK2* mutation or α -synuclein multiplication.

Table 2. Patient Characteristics and Clinical Evaluation Results at Latest Follow-up

	Patient 7	Patient 15
Follow-up, y ^a	18	15
Age, y/disease duration, y	67/28	69/27
Genetic tests	No mutations for all known PD genes (including Parkin, <i>PINK-1</i> , and <i>DJ-1</i> as well as MLPA analysis to exclude presence of the G2019S <i>LRKK2</i> mutation or α -synuclein multiplication)	No mutations for all known PD genes (including Parkin, <i>PINK-1</i> , and <i>DJ-1</i> as well as MLPA analysis to exclude presence of the G2019S <i>LRKK2</i> mutation or α -synuclein multiplication)
PD-related medication	Amantadine, 300 mg/d; buspirone, 15 mg/d	Amantadine, 300 mg/d; trihexyphenidyl, 2.5 mg/d
UPDRS score		
Part III total (range, 0-108) ^b	22	18
Part II total ADL (range, 0-52)	11	15
Part IV.A dyskinesias (range, 0-13)	3	7
Part IV.B fluctuations (range, 0-7)	0	2
AIMS total score (range, 0-42) ^b	16	11
PDQ-39 SI (range, 0-100)	11.2	31.8
NMSQ (range, 0-30)	7	10
MMSE (range, 0-30)	30	30

Abbreviations: ADL, Activities of Daily Living; AIMS, Abnormal Involuntary Movement Scale; amantadine, amantadine hydrochloride; buspirone, buspirone hydrochloride; MLPA, multiplex ligation-dependent probe amplification; MMSE, Mini-Mental State Examination; NMSQ, Non-Motor Symptoms Questionnaire; PD, Parkinson disease; SI, summary index; trihexyphenidyl, trihexyphenidyl hydrochloride; UPDRS, Unified Parkinson's Disease Rating Scale.

^a From first graft.

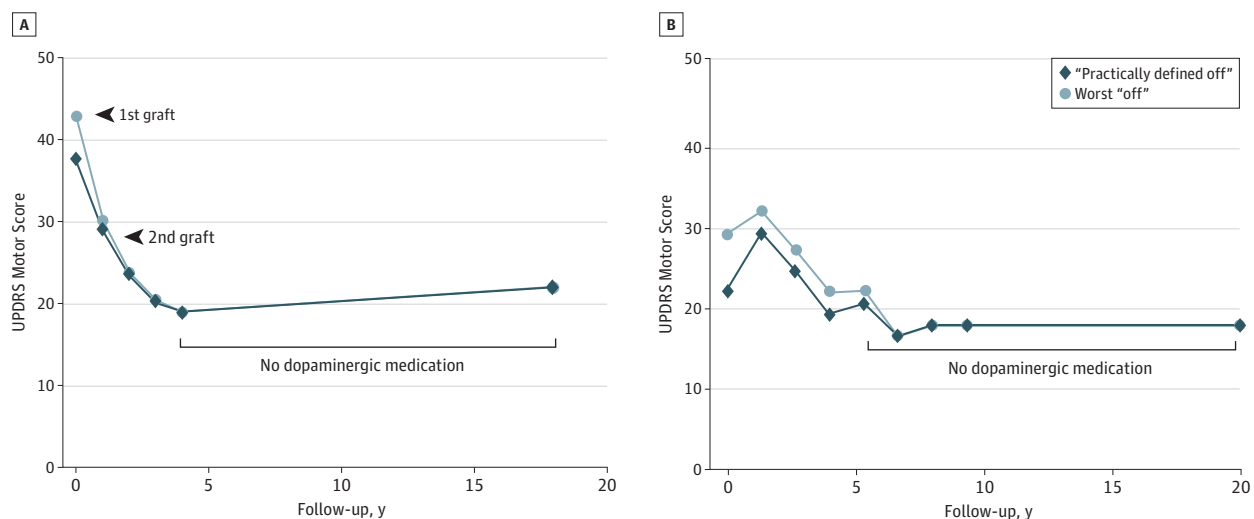
^b Patients were assessed without (overnight withdrawal) and 1 hour after taking their contemporary PD-related medication (no dopaminergic agents included). Both conditions provided identical results and thus are presented as single scores.

Results

Following transplantation, patient 7 experienced significant motor benefits, which gradually emerged over the course of 4 years. He was able to stop levodopa treatment 26 months after the first transplantation, by which time the "on-off" phenomena had virtually disappeared and his practically defined "off" motor UPDRS score had decreased by 38% compared with baseline score. By the fifth postoperative year, all dopaminergic agents had been withdrawn while the patient's motor status continued to improve. At his last assessment, 18 years postgrafting, the patient demonstrated sustained motor benefits, scoring 22 on the UPDRS motor examination, reported no fluctuations, and remained free of any pharmacological dopamine replacement therapy. The patient continues to be independent in all activities of daily living (**Table 2** and **Figure 1A**). While his speech remains dysarthric and hypophonic, his swallowing is normal, and falls or freezing have not emerged as a problem.

Postoperatively, this patient reported dyskinesias during "off" medication phases (graft-induced dyskinesias [GIDs]).⁷

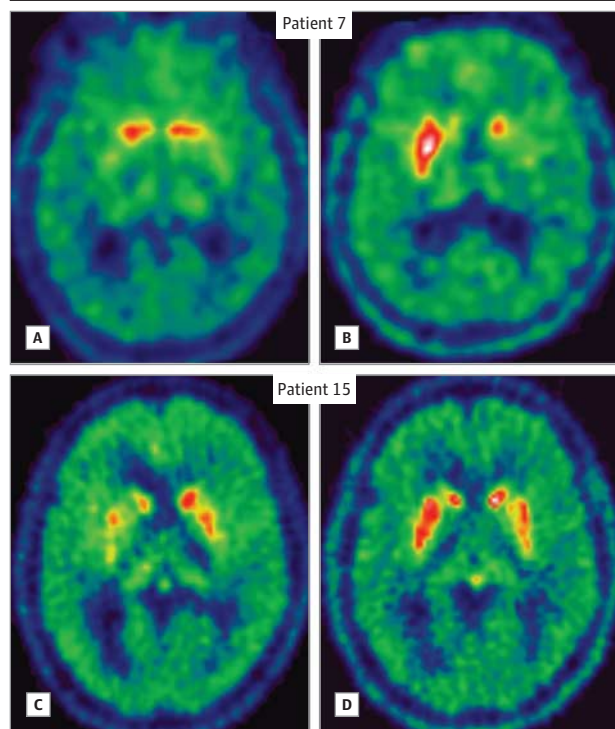
Figure 1. Motor Scores Before and After Transplantation



Motor scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) during “off” phases for patients 7 (A) and 15 (B) pretransplantation (point O) and at different follow-up times posttransplantation: “practically defined off”; morning

motor evaluations after 12-hour withdrawal of Parkinson disease medication; and worst “off.” Motor evaluations to reflect severity of motor disability documented at other points during an inpatient admission.⁵

Figure 2. 6-L-Fluorodopa F 18 Positron Emission Tomography Images Before and After Transplantation



Fetal mesencephalic grafts restored dopaminergic innervation in the striatum of 2 patients with Parkinson disease. The images portray striatal uptake before (A and C) and after (B and D) transplantation for patients 7 and 15.

Levodopa-induced dyskinesias were still present following levodopa administration, prompting reduction in levodopa replacement therapy, which successfully led to their improve-

ment. In the early postoperative years, GIDs persisted despite discontinuation of all dopaminergic agents, were mild to moderate in severity, and caused no distress or disability. Nonpainful dystonic posturing of his right foot also developed after transplantation. At the most recent follow-up, he had GIDs of moderate degree that he felt were to some extent helped by amantadine hydrochloride and buspirone hydrochloride.⁶ His GIDs were still less severe in comparison with his LIDs pretransplantation. His left foot dystonia partially interfered with his walking, which, nonetheless remained independent and safe, with good arm swing bilaterally.

During the first 2 years after transplantation, patient 15 showed no improvement in UPDRS motor scores in the “practically defined off” state. However, “on” periods were prolonged and the patient’s self-reported frequency and severity of motor fluctuations diminished, allowing a 66% reduction in his daily levodopa equivalent dose.⁸ Improvements in motor function became more evident from the fourth year postgrafting, by the end of which he was able to stop all dopaminergic medication, given that “on” and “off” conditions were almost indistinguishable. Assessment 15 years posttransplantation demonstrated preserved motor benefits (Figure 1B). During the motor examination, the patient had minor rigidity and bradykinesia, normal gait, and intact postural reflexes. He remained free of dopaminergic medication. He was aware of some diurnal variation of his motor function but remained independent in all activities of daily living (Table 2). Freezing and falls were frequent before grafting, even during the “on” condition, whereas the patient now reports very rare freezing episodes and no falls.

During the first postoperative year, his LIDs markedly decreased in severity and duration, but the patient noticed spontaneous dyskinesias independent of levodopa intake. These have persisted over the ensuing years but have had no func-

tional impact. At the latest follow-up assessment, the patient's GIDs mainly involved his legs and were of mild to moderate severity. The patient found that these were only modestly helped by amantadine. Graft-induced dyskinesias (despite being his major current concern) remained milder than the severe biphasic and peak-of-dose LIDs he experienced pregrafting, which sometimes forced him to lie on the floor.

The Non-Motor Symptoms Questionnaire revealed a number of nonmotor symptoms for both patients that did not require pharmacological treatment (Table 2). While nonmotor questionnaires were not used pretransplantation, so that direct comparison is not possible, most of the current nonmotor concerns had also been present prior to grafting. At latest neuropsychological assessment, patient 7 had evidence of some decline in executive function (semantic verbal fluency and Trail Making Test) and episodic memory and learning of words. Patient 15 had evidence of some decline in executive function (Wisconsin Card Sorting Test, phonemic verbal fluency, and Stroop Test), episodic memory and learning of words, and attention. Nevertheless, there was no indication of any clinically significant cognitive decline. At the time of the latest follow-up, the Mini-Mental State Examination score was 30 of 30 in both patients.

No coding mutations were identified in any of the extensive genetic tests performed for either patient (Table 2). In line with the clinical postoperative improvements, an increase in striatal ^{18}F -Dopa uptake was observed after transplantation (Figure 2).

Discussion

This study presents the very long-term clinical outcomes in 2 patients with PD treated with intrastriatal fetal ventral mesencephalic grafts. Clinical assessments 18 and 15 years posttransplantation demonstrate sustained benefits, with motor scores still lower than their preoperative baselines. Despite each patient having nearly 30 years of PD with troublesome fluctuations and dyskinesias prior to transplantation, both patients now present with very mild symptoms and have been independent of any pharmacological dopaminergic treatment for more than 10 years. Neither patient had axial impairment nor dementia despite the presence, in patient 15, of freezing and falls prior to transplantation, features that often herald a progressive decline in independent function.^{8,9} These data are of course uncontrolled; therefore, the very long-term clinical natural history of their disease in the absence of surgery cannot be reliably inferred. However, the sustained motor benefits agree well with the gradual, complete normalization of ^{18}F -dopa uptake (as a measure of dopaminergic innervation) and carbon 11-labeled raclopride binding (as a measure of drug-induced dopamine release) in the grafted putamen of both patients.⁶ Moreover, the course of PD is generally relentlessly progressive, and the limited progression of disability in these 2 individuals since grafting is not usually achieved by other conventional therapeutic strategies.⁹ It is well recognized that, in some subjects with young-onset disease and recessively inherited parkinsonism due to Parkin mutations, disease may

progress relatively slowly. However, our patients actually improved, as opposed to progressing slowly, and full testing for such mutations was negative in both of these patients (Table 2). Possible factors that may relate to the prolonged remarkable beneficial effects of transplantation seen in these patients are their young age at onset, preserved preoperative ventral striatal dopaminergic uptake, and preserved levodopa response.¹⁰⁻¹²

There are, however, a number of points to be made in relation to these observations. These patients represent 2 of a total of 18 patients (3 were cases with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism) who received fetal cell transplantation in Lund, Sweden, on an open-label basis from the late 1980s to the mid-1990s. Short- to mid-term outcomes have been previously reported in detail.^{3,4} An overview analysis of the results of the whole cohort has been presented by Lindvall and Björklund¹³ and in a meta-analysis article by Barker et al,² showing variable but overall favorable outcomes posttransplantation. In addition to the 2 individuals described in the current study, at least another 2 of this cohort (patient 4 and patient 13) were reported to have an equally favorable outcome 10 or more years posttransplantation.^{14,15} The remainder of the cohort have either died or been lost to long-term follow-up.

Graft-induced dyskinesias occurred in both patients but did not have a significant functional impact and their occurrence was outweighed by the beneficial effects on motor function gained over the years. Nevertheless, GIDs represent a serious adverse event that can be debilitating but seem to be helped by deep brain stimulation of the internal segment of the globus pallidus.^{7,11,12,14-17} Neither patient has been sufficiently troubled by their GIDs to consider pallidal deep brain stimulation as a treatment. Undoubtedly, understanding and finding ways to avoid GIDs remains of major importance for the future of dopaminergic cell therapies.^{6,7,15}

Postmortem studies of brains from patients with PD receiving fetal neural grafts over a decade prior to death have shown that some of the grafted dopamine neurons exhibit Lewy bodies.^{18,19} Although the proportion of cells displaying Lewy bodies is only reported to be in the range of 2% to 8%, as many as 80% exhibit increased levels of soluble α -synuclein in the cell bodies, a change consistent with premature aging of the cells. More detailed follow-up studies suggest that over time some of the grafted neurons progressively express reduced levels of the dopamine transporter and tyrosine hydroxylase, which further supports the notion that the disease process directly impacts the grafted cells.²⁰ It is likely that the 2 cases described in this report also have similar changes in their grafted neurons. In that context, it is particularly encouraging that the grafts still continue to exert positive functional effects.

The gradual emergence of clinical improvements in both patients, albeit anticipated given the nature of the intervention, is highly relevant with respect to future cell therapy trial designs, particularly in relation to the variable long-term natural history of PD. It may be that the major effects of dopaminergic cell replacement with respect to motor and nonmotor symptom control only become fully apparent with long-term follow-up. Whether future transplantation protocols should

also target extrastriatal nondopaminergic systems to achieve more widespread benefits in motor and nonmotor features of PD not dopaminergic in origin remains a subject under consideration.²¹ In this report, we are aware that only 2 individuals are included and that these represent 2 particularly successful cases, and thus, any conclusions should be drawn with caution. Nevertheless, we would suggest that these patients,

together with a few other cases exhibiting similarly long-term favorable outcomes, provide support that dopaminergic cell transplantation may offer a substantial and very long-lasting compensatory effect in PD.^{6,14,15} Our results provide encouragement for basic science and clinical studies that strive to develop a clinically competitive stem cell-based dopaminergic cell therapy for PD.

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Analysis and interpretation of data: All authors.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Kefalopoulou, Brundin.

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Conflict of Interest Disclosures: Dr Brundin owns shares in the company ParkCell AB, which aims to develop a transplantation therapy for PD by using skin-derived cells. No other disclosures were reported.

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