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Long-term Clinical Outcomes After Fetal Cell Transplantation in Parkinson Disease
Implications for the Future of Cell Therapy

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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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In the late 1980s, when a moratorium had been imposed on US federal financing for all medical research involving fetal tissue, one of the first open-label trials of fetal dopaminergic cell transplantation in Parkinson disease (PD) was undertaken by researchers in Lund, Sweden. Nearly 30 years since the first patient was enrolled, the topic of cell transplantation in PD has transformed, with a handful of open-label trials, 2 sham-controlled studies, and a great deal of academic controversy. The report in *JAMA Neurology* by Kefalopoulou et al[1] describes the positive long-term clinical outcome of 2 participants from the original Lund transplantation study. This represents the longest clinical follow-up data available on mesencephalic transplanted cells in the PD population. The observations presented in this report are important but anomalous of the existing body of data on the topic of cell transplantation in this field. Furthermore, data from graft studies may have implications for stem cell–derived transplants in the future; thus, the authors' warning that "any conclusions [from the observations presented here] should be drawn with caution" is well heeded.

Studies of cell replacement therapy with fetal grafts of ventral mesencephalic tissue have provided proof of concept that nonviable dopaminergic neurons can be replaced by new neurons that reinnervate the striatum and release dopamine.[2,3] The successful integration and survival of grafted cells has been confirmed using fluorodopa-uptake scans and with pathological studies, but attempts to correlate these changes with clinical outcomes have been largely disappointing. Among the cohort of 18 patients in the Lund study, from which these 2 patients were derived, there were substantial differences in short-term motor outcomes between patients, and long-term follow-up data could be obtained on only a few.[1] A handful of other open-label studies around the same time reported results that were mostly positive but similarly variable, with many patients lacking any motor improvement after transplant.[2] Later, 2 sham-procedure controlled trials of fetal cell transplants were conducted: one of these demonstrated modest improvements in motor outcomes at 4 years after surgery, but the other showed no difference compared with sham procedure.[2,3] These differences in outcomes between studies are often attributed to methodological differences among them[4]; to this point, a novel multicenter open-label clinical grafting trial sponsored by the European Union (TRANSEURO) aims to address and reconcile several concerns raised by these inconsistent data.[5] Specifically, there is hope that this trial will address the important issues of appropriate patient selection, tissue placement, and trial design, which may optimize fetal grafting and have future relevance for stem cell transplantation.

The observations presented in the current case series by Kefalopoulou et al[1] represent only a tenth of the original patients in the Lund study and an even smaller proportion of all patients who have received transplantation in the various open-label and sham-controlled trials. Nevertheless, the observations reported here are important and unexpected. The authors describe 2 patients with

young-onset PD who were followed up at 15 and 18 years after transplant, respectively. These 2 individuals were able to remain free of medication and had minimal (if any) motor disease progression over the extended period of observation. This is surprising given the progressive nature of PD, and it is tempting to attribute this to a disease-modifying or neuroprotective effect of the treatment intervention. These results are particularly noteworthy in the setting of data from some postmortem studies that have shown the presence of pathologic Lewy bodies involving grafted neurons, suggesting that disease progression not only continues after transplantation, but also spreads to involve the transplanted cells.[6]

Clinically, it has become clear that subtypes of PD exist with variable responsiveness to medication, variable rates of progression, and variable extents of pathology. Whether the 2 cases reported represent clinically unique variants of PD or whether they represent neuroprotective effects of the transplant cannot be determined from this limited sample. If they do represent disease-modifying effects, then the successful outcomes presented underscore the importance of ongoing investigations to optimize patient selection variables for transplantation, as certain factors such as young age at onset and PD subtype are likely crucial to the differences in outcomes reported among the different studies. Practically, identifying factors that predict positive clinical outcomes from fetal cell transplantation may be most relevant for the future of stem cell programs.

Most investigators agree that fetal cell transplantation is unlikely to become a mainstream treatment for PD because of limited tissue availability and issues with standardization of grafts. Both the generation of dopaminergic neurons from stem cell–derived progenitors, and the reprogramming of fibroblasts into pluripotent cells, or even directly into dopamine neurons, will potentially enable researchers to transplant large numbers of neurons into large numbers of patients. Assuming the growth, functionality, and survival of these cells can be optimized, and the techniques validated, there are still practical limitations unique to PD that will need to be addressed before transplantation of neurons obtained from cellular reprogramming can be translated to the clinical setting. Parkinson disease is unique among neurodegenerative disorders in that life expectancy is relatively normal, and available pharmacologic therapy is extremely valuable in treating motor symptoms. Therefore, for a new therapy to be considered clinically useful, it must offer better outcomes than existing therapies and have low potential for serious adverse events. With the exception of the cases described herein, trials of fetal graft therapy have failed to demonstrate results that exceed the motor benefits or adverse effect profile of deep brain stimulation (DBS). Of particular concern with cell transplants is the risk of developing intractable dyskinesias (as seen in these cases), which in some studies affect more than 50% of study participants; this risk must be minimized (potentially by selecting patients without levodopa-induced dyskinesias to begin with) before cell transplantation can be practically implemented.

The TRANSEURO trial will hope to clarify some of the discrepancies in the literature on cell transplant in PD by addressing some of the methodological problems of prior studies, but more definitive placebo-controlled trials will be needed. Future trials will likely require the use of reprogrammed cells as donor tissue, as it is difficult to standardize the cell preparations obtained from fetal tissue when studying large series of patients. Moreover, the location of the graft in relation to the disease stage may make a difference, and future studies will need to consider whether cell transplantation outside the striatum, and even transplantation of nondopaminergic neurons, may be beneficial given the diverse and often widespread nature of the pathology in PD. Even if the symptomatic benefit of cell transplantation can be reproduced in a placebo-controlled study, the practical implementation of such a technique in the setting of existing proven therapies such as DBS will rely on demonstration of disease-modulating effects such as those suggested by this case series. The development of new cell models of PD generated from stem cells, in addition to existing animal models, may allow for more targeted neuro-restorative therapies that combine cell transplantation techniques with gene therapies and neurotrophic factors. For now, the controversy surrounding cell-based transplantation therapy for PD continues, as there is no fast track to the safe and thoughtful clinical implementation of these techniques.

ARTICLE INFORMATION

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