

What are the long-term effects of neural grafting in patients with Huntington's disease?

Original article Bachoud-Lévi AC *et al.* (2006) Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. *Lancet Neurol* 5: 303–309

SYNOPSIS

KEYWORDS brain metabolic activity, clinical outcome, Huntington's disease, neural transplantation

BACKGROUND

Transplantation of human fetal neuroblasts into the striatum has been shown to improve motor and cognitive function in some patients with Huntington's disease, but the long-term effects of neural grafting are not known.

OBJECTIVE

To describe the time course of clinical benefits and improvements in resting brain metabolism over a long period in patients with Huntington's disease who received fetal neural transplants.

DESIGN AND INTERVENTION

In a recent pilot study, five patients with Huntington's disease received grafts of human fetal neuroblasts; grafts were implanted first into the right striatum and then, after 1 year, into the left striatum. The patients were assessed each year using the Unified Huntington's Disease Rating Scale (UHDRS), MRI, and neurophysiological and neuropsychological tests. In addition, resting cerebral activity was recorded at 2 and 6 years using 2-[¹⁸F]-fluoro-2-deoxyglucose-PET (FDG-PET). A preliminary analysis conducted 2 years after the first implant showed improved or maintained motor and cognitive function in three patients; furthermore, brain activity in the frontal and prefrontal cortices of these patients was fully recovered. The current report presents the 6-year follow-up results for these three patients.

OUTCOME MEASURES

The primary outcome variables were the neuropsychological performance and the resting cerebral activity.

RESULTS

Chorea remained stable at an improved level for 6 years in two patients and for 4 years in one patient, compared with preoperative values. A plateau phase was also observed for oculomotor symptoms, tapping, and gait parameters such as retropulsion and walking, after which these motor symptoms deteriorated variably. The severity of dystonia steadily increased throughout the whole follow-up period in two patients, and began to increase after 4 years in the third patient. Performance remained stable on neuropsychological tests that were not timed, such as those evaluating language comprehension or global intellectual abilities. By contrast, performance on timed tests deteriorated during the follow-up period, indicating a progression of motor disability. The MRI hypsignals associated with the striatal grafts remained unchanged during long-term follow-up, indicating that the grafts remained functional. FDG-PET revealed that glucose consumption in the frontal and prefrontal cortex remained stable for 6 years in all three patients, but in surrounding brain areas there was an increase in hypometabolism during the follow-up period.

CONCLUSION

Neural grafting in patients with Huntington's disease helps to preserve time-independent cognitive tasks for a period of up to 6 years. By contrast, tasks that need a controlled movement deteriorate steadily after an initial period of stabilization. The findings also indicate that implants of fetal neural tissue can substitute for lost cell populations, but they might not adequately prevent the progression of neurodegeneration in other areas of the brain.

COMMENTARY

Ole Isacson

Detailed genetic information is available for several neurological diseases characterized by regional neuronal loss, including Huntington's disease, but these genetic findings have not yet produced new treatments for patients, although they have improved the diagnosis.^{1,2} In Huntington's disease, there is a genetically predetermined process causing death of neurons within the patient's caudate-putamen (striatum). Transplanted neural tissue (neurons and glia progenitors) lacking the mutated gene can replace the disease-prone neurons and create new functional connections. Such cell transfer can also potentially slow down neurotoxic processes by the release of neurotrophic factors from the transplanted cells.³ In the future, neural replacement could perhaps be combined with other factors that promote regeneration and recovery of function.

Anne-Catherine Bachoud-Lévi and co-workers implanted patients with Huntington's disease with human fetal striatal tissue obtained after abortion. Such tissue contains post-mitotic neural tissue and cells programmed to become neurons and glia in the striatum and globus pallidus. In their previous report, 2 years after implantation, the authors noted several positive effects of the implants on cognition, chorea and dystonia, which were accompanied by improved cortical metabolic activity.⁴ The current report covers the follow-up period from 2 to 6 years after neural transplantation in patients who experienced positive effects. The investigators found that although the chorea and cognition were still relatively improved, dystonia had become a dominant feature.

This is a unique exploration because of the long time frame of 6 years post-implantation. The earlier publication by this group showing improvements at 2 years with a correlate of improved PET-scan metabolic activity in the cortex—a distant interacting target with the striatum—is interesting. The cortical metabolic activity might reflect both motor and cognitive reconnection effects. Given that cell therapy using fetal, progenitor or stem-cell-based technology is not by any means optimized,

future clinical trials should employ variations in graft placements and donor tissue amount, and provide data on the variables that can be controlled to use this restorative treatment for brain disease. The present study lends optimism to future implantation trials evaluating replacement of the neurons and cells that are most vulnerable to the disease process. Another previous clinical trial in patients with advanced Huntington's disease demonstrated that the implanted striatal neurons are not affected by the disease process after implantation.⁵ The current article illustrates, however, that disease progression continues despite restorative treatment. Previous experience indicates that neurotransmitter release functions are likely to be restored in conjunction with the neurotrophic effect on host circuitry. Loss of normal huntingtin activity—the major defect underlying Huntington's disease—leads to a reduction in the levels of brain-derived neurotrophic factor in the striatum, and the transplantation of unaffected cells might restore such neurotrophic deficits by neuron-target interactions (for example, of cortex with striatum).²

This study emphasizes the potential of neurotransplantation as a restorative treatment for Huntington's disease, and also correctly concludes that a combined effort might be necessary in the treatment of patients with this disorder, including genomic, pharmacological and cell-restorative modalities.

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Competing interests

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PRACTICE POINT

This long-term follow-up study indicates that neurotrophic and cellular technologies might be future modalities for the treatment of patients with Huntington's disease, but yields insufficient data to influence current clinical practice