Neural Transplantation for the Treatment of Huntington's Disease

Roger A Barker[1] and Rachel A Swain[2]

1. Reader in Clinical Neuroscience and Honorary Consultant in Neurology, Addenbrooke's Hospital;
2. Research Assistant, Cambridge Centre for Brain Repair, University of Cambridge

Abstract

Neural transplantation studies where foetal striatal tissue is grafted into the striatum of patients with Huntington's disease have taken place at several sites worldwide in recent years, following success in rodent models of the disease. Studies have for the most part been safe but have had various degrees of effectiveness. This article looks at the successes and failures of these studies and considers what has been learnt in terms of safety, techniques and methodology. While knowledge of the optimal protocol is advancing, there are still many aspects that need refining, such as immunosuppression and grafting technique. Although advances in this field are hampered by the need for more complete knowledge of the disease itself, the future of neural transplantation has a great deal of potential.

Huntington's disease (HD) is a progressive neurodegenerative disorder that is inherited and characterised by involuntary movements, psychiatric and cognitive symptoms and signs. It is caused by an expansion of the CAG repeat in exon 1 of the huntingtin gene. Patients with 36 or more CAG repeats in this gene develop HD; this abnormal expansion results in the production of mutant huntingtin, which has a toxic gain-of-function leading to the formation of intracellular protein aggregates followed by neuronal dysfunction and death. This occurs at many sites in the central nervous system, but with an early predilection for the striatum and cerebral cortex. The condition is currently incurable and patients typically succumb to the disorder about 20 years after disease onset.[1] This fatal outcome, coupled with the absence of any disease-modifying therapies and focal pathology, at least at disease onset, has made this disorder a target for neural transplantation, with the main target being the striatum. Prior to clinical trials, transplantation of appropriately aged foetal striatal tissue had shown safety and efficacy in rodent and primate models of HD,[2–4] albeit in non-transgenic models of disease. This led to a number of small open-label trials, which are the subject of this article (see Table 1 for a brief summary).

Results of Huntington's Disease Trials

Kopyov et al., Los Angeles[5]

One of the earliest trials transplanted three moderately advanced patients bilaterally with one-year follow-up using a non-core assessment programme for intracerebral transplantation in HD (CAPIT-HD) protocol. While the authors reported no motor improvement post-grafting, magnetic resonance images (MRIs) showed evidence of graft survival on average 45 weeks after transplantation.[6] Post-mortem studies on two of the patients have now been reported. The two patients died 74 and 79 months after transplantation[7] and received transplants along six and eight different tracts through the striatal complex, respectively. At autopsy, 13 of the 14 grafts were identified, with little evidence of integration of the grafted tissue into the host brain. In some cases, aberrant growth of some tissue elements within the transplant was seen. The authors gave several explanations for this, including the possible requirement for a primitive or foetal-like environment for graft maturation and integration, which is therefore compromised in the degenerating HD brain. The authors reported no signs of HD pathology in the grafts.

A third patient had an autopsy 121 months after the intracerebral transplantation. This revealed multiple cysts. The authors attributed this to the presence of a sural nerve cograft, since overgrowth was not observed in any other autopsy study.[8]

Bachoud-Lévi et al., Creteil[9,10]

This group carried out first unilateral and then, one year later, contralateral transplants in five patients with HD. Patients have been followed up according to the CAPIT-HD protocol for six years, with some post-mortem data after 10 years. The authors have compared this data with a cohort of 22 non-grafted patients.

Three of the five patients showed clinical improvement, a fourth showed an initial improvement that was lost suddenly after the second graft (due to the development of a putaminal cyst) and a fifth

progressively declined. In patients who improveed, individual improvements in motor function continued for two years after transplantation and then remained stable for several years before deteriorating four to six years postgrafting. While the transplant had no effect on dystonia, which deteriorated consistently, chorea remained at a stable level for between four and six years after surgery. The authors attribute this to the lower number of tracts in the posterior putamen compared with the caudate nucleus and anterior putamen. This is in contrast to Rosser et al.[11] (see below), where dystonia varied between grafted patients and chorea progressively increased (unpublished data).

Further investigation of graft integration in these patients was performed using electrophysiological recording of the N20 wave produced in the somatosensory cortex upon median nerve stimulation. While reappearance of this wave, once lost, was never observed in the cohort of non-grafted HD patients, bilateral recovery of the N20 wave did reappear in three of the transplanted patients (though it was lost in one patient after the second transplant).

For six years after transplantation there was a slower decline in striatal metabolic activity compared with non-transplanted patients. Furthermore, normal metabolic activity was restored and maintained in frontal and prefrontal cortices for six years post-operatively, showing that cortical hypometabolism is reversible, at least in early HD.[10,12] This effect was only seen in the three patients who showed clinical improvement.

Antibody assays in patients from this series of transplants showed evidence of alloimmunisation to donor antigens, which in one case lead to graft rejection.[13]

Hauser et al., Florida[14]

In this study seven moderately-advanced HD patients were transplanted bilaterally with tissue derived from the lateral parts of two to eight foetal lateral ganglionic eminences. This selective dissection was done to try and enhance the yield of striatal tissue relative to the other tissue that takes its origin from the developing striatal eminences, though there were limited experimental data to support such a dissection. Three patients suffered subdural haemorrhages perioperatively and two actually required further surgeries for this.

When all seven patients were considered there was no significant difference in Unified Huntington's Disease Rating Scale (UHDRS) scores before and 12 months after surgery. A post hoc analysis, excluding the patient who suffered the worst subdural haemorrhage, showed significantly lower UHDRS scores 12 months after transplantation. Positron emission tomography (PET) imaging one year after transplantation showed no significant change in striatal metabolism or in D1 or D2 receptor binding compared with normative data.[15]

Post-mortem studies of these patients have shown surviving grafted cells 18 months after transplantation in one deceased patient (although not in the caudate) and in only two out of three patients 10 years post-grafting.[16,17] Where survival of cells was seen, the grafted striatal tissue appeared unhealthy and the medium spiny neurons of the graft had degenerated more than interneurons, mirroring to a degree that seen in the striatum of patients dying with HD. This led the authors to conclude that the striatal transplant may have followed

Table 1: Summary of the Main Transplant Trials Carried Out to Date

Study	Number of Patients	Age of Foetal Implant	Amount and Area Implanted	Immunosuppression Treatment	Length of Clinical Follow-up	Efficacy	Imaging MRI	Imaging PET	Post-mortem
Kopyov et al., 1998[5]	3	8–10 weeks	5–8 foetuses per side (LGE)	None reported in original paper, though cyclosporine had been used in the two autopsy patients for 18 and 35 months[7]	12 months	No detailed follow-up carried out	Tracks/graft targets seen[6]	Not reported	2 patients at 74 and 79 months after grafting; some striatal tissue survival, little integration.[7] 1 patient at 121 months post-grafting; cysts present though probably due to sural nerve co-graft[8]
Bachoud-Lévi et al., 2000[10]	5	7.5–9.5 weeks	Equivalent to 1 foetus (WGE)	Cyclosporine prednisolone (1 year), azathiprine (1 year)	72 months	Clinical improvement in 3 of 5 patients 2 years after transplant, maintained for 4–6 years after surgery (compared with non-grafted patients)	Hypo-intense signal at graft sites for 6 years	FDG PET: restored and maintained metabolic activity for 6 years, only in improved patients[10,12]	None reported
Hauser et al., 2002[14]	7	8–9 weeks	2–8 striatum per side (Lateral part of LGE)	Cyclosporine (6 months)	12 months	No overall difference in UHDRS scores before and 1 year after transplant	None Reported	D_1R: no change. D_2R: no change in rate of decline, as normally seen in HD[15]	4 patients: Graft survival at 18 but only 2/3 at 10 years. Grafts show HD-like pathology at 10 years[16,17]
Rosser et al., 2002[11]	4	8.5–12 weeks	1–2 foetuses per side (WGE)	Cyclosporine A, azathioprine and prednisolone until 1 year post-transplant	6 months	No significant difference in UHDRS scores 6 months after transplant compared with non-grafted patients	Tracks/graft targets seen	D_2R: no change in rate of decline, as normally seen in HD	None Reported
Reuter et al., 2009[19]	2	9–10 weeks	2–3 foetuses per side (WGE)	Prednisolone (1 month), cyclosporine (1 year)	60 months	Radically improved UHDRS score in 1 of 2 patients at 5 years after transplant	None Reported	D_2R: increased binding at 2.5 years post transplant (last PET scan)	None reported
Gallina et al., 2008[20,21,22]	4	9–12 weeks	2 foetuses per side (WGE)	Methylprednisolone (2 weeks), cyclosporine A (1 year), azathioprine (continuing)	Mean 24.7 months	UHDRS score stabilisation or slight improvement at 2 years (no comparison with non-grafted patients)	Tracks/graft targets seen	D_1R: increased in 3 out of 4 patients	None reported

D_1R = D1 receptor binding; D_2R = D2 receptor binding; FDG = ([18F]-fludeoxyglucose; HD = Huntington's disease; LGE = lateral ganglionic eminence; MRI = magnetic resonance imaging; PET = positron emission tomography; UHDRS = Unified Huntington's Disease Rating Scale; WGE = whole ganglionic eminence.

the same fate as the diseased striatum of the HD recipient, which has obvious implications for the use of neural transplantation.

Of relevance to this debate is the observation from another, unrelated, study in Germany that followed the CAPIT-HD protocol. Here, graft survival and integration was observed six months after transplantation.[18] Thus, there is good evidence for short-term, but not necessarily long-term, survival of grafted foetal striatal tissue.

Rosser et al., The European Network for Striatal Transplantation in Huntington's Disease[11]
In the NEST-UK study, four patients with mild to moderate HD were given unilateral foetal striatal allografts, followed an average of 22.5 months later by a second transplant to the contralateral striatum. A fifth patient received simultaneous bilateral transplants. The initial report showed that this approach was safe and more recently data have emerged about the efficacy of this approach (Barker et al., unpublished data).

Patients were compared to a group of 12 non-grafted patients with HD and were followed up according to the CAPIT protocol for three to nine years. One patient died of unrelated causes eight years after his second transplant. Non-statistically significant improvements in motor function were observed two years after transplantation compared with non-grafted HD patients. No significant impact on the rates of decline in striatal [11-C]Raclopride binding potential was observed, in line with the clinical findings.

Reuter et al., London[19]
Two patients with moderate HD were given bilateral striatal transplants and compared to a group of six non-grafted controls according to the CAPIT-HD protocol. While one patient showed marked improvement, the other deteriorated at the same rate as non-grafted patients.

The improved patient lost 46 points on his UHDRS motor score over five years. Cognitive tests, such as verbal fluency, however, improved in the first three years. [11-C]Raclopride PET scanning in this patient showed increased striatal D2 binding six months after transplantation, which remained higher than the preoperative level when he was last scanned 2.5 years post-grafting. Since this time, the patient has had no more PET scans. It is likely that he improved because he was grafted with three times as much foetal striatal tissue as was employed in the Rosser et al. study.

Gallina et al., Florence[20–22]
This study transplanted four HD patients bilaterally with two whole lateral ganglionic eminences per hemisphere and followed the CAPIT-HD protocol, although no non-grafted patient data were used as a comparison. The authors reported small improvements or stabilisation in UHDRS scores a year after transplantation, which lasted for two years in two of the four patients.

MRI and PET imaging data were combined to present evidence for integration of metabolically-active grafted tissue in six of eight grafts six to nine months after transplantation.[22] The level of hyperactivity then declined, but remained higher than preoperative levels.

[123I]Iodobenzamide single photon emission computed tomography imaging showed increased D2 receptor binding in three out of four patients (at 18 to 24 months after transplantation). Grafted tissue was detected not only in the striatum but also in the frontal cortex, which the authors suggested could be evidence for migration of grafted cells, but more likely reflects tissue misplacement or reflux up the transplant tract.[21]

What Has Been Learned?
Safety
Almost all of the studies report that foetal transplantation in HD is safe. The exception is the study by Hauser et al.,[14] which reported subdural haemorrhages in three out of seven patients. This is most likely due to the greater degree of cerebral atrophy owing to the more advanced nature of these patients, which expands the subdural space and predisposes them to subdural haemorrhages after surgery. The overgrowth reported in one of the patients in the Kopyov study was thought to be due to the sural nerve cograft and not to the striatal grafts, which alone have never been shown to result in overgrowth.[8] Similar overgrowth has not been reported in animal models of Parkinson's disease (PD) nor in PD patients receiving adrenal medullary and sural nerve cografts.[23,24]

Immunosuppression
Despite the commonly held view that the brain is immunologically privileged, there does appear to be a need for immunosuppression. This view is supported by data from both animal models of HD transplantation and clinical PD transplant trials. The optimal method of immunosuppression has yet to be defined, though, as does the way to ensure that patients are compliant in taking therapy.[9] Triple immunosuppression, as used for whole-organ transplants,[10,11,21] may best prevent rejection, although single immunosuppression may well be sufficient and have fewer unwanted side-effects.[14]

The length of time immunosuppression is continued is also important. The lack of efficacy in the Hauser et al. study[14] may be explained by the short use of ciclosporin A (six months), as has been reported in some negative PD clinical trials.[25]

Recent studies have further emphasised the importance of immunosuppression. In the French study, antibodies caused by alloimmunisation were found in four out of 15 transplant patients and caused graft rejection in another.[26] This is the only case of actual rejection, although some autopsy studies have found evidence of an immune response at the transplant site at six months and 10 years when triple immunosuppression and ciclosporin alone had been used, respectively, post-grafting.[18,17] Other autopsy studies have in contrast reported minimal immune response at 18 months[16] (the same series as autopsy at 10 years[18]) and at seven and 35 months (using ciclosporin only).[7] This difference could be due to the natural variability between grafted patients, but may reflect a long-term immune reaction to the graft, which has implications for the length of immunotherapy required in such studies. It may be that an immune response is mounted in the first few months after transplantation, no matter what the type of immunosuppression given, and this may be driven as much by the grafting procedure as by the specific tissue being used. In some cases this may not subside and a chronic low-grade rejection process will be induced.

Finally, it is worth noting that the immunosuppressant drugs themselves may have a direct effect on the disease course, as ciclosporin A has been shown to have some direct neuro-restorative effects.[27]

Techniques
Factors Affecting Foetal Tissue
Age
There are several critical factors surrounding the transplantation of foetal tissue; one of the most obvious being its age. The authors of the study in Italy[21] report that there is some evidence a slightly older gestational age of nine to 12 weeks produces better results. Indeed the Reuter et al. study produced very good, long-lasting results in one patient when tissue aged nine to 10 weeks was used rather than tissue of seven to eight weeks, as used in other studies.[19]

Source
All of the European studies following the CAPIT-HD protocol transplanted the whole ganglionic eminence. In contrast, Kopyov et al. used just the lateral ganglionic eminence (LGE),[5] while Hauser et al. used just the lateral half. Thus, while LGE grafts have been shown to produce higher proportions of striatal-type cells, it seems that striatal interneurons from the medial ganglionic eminence are also vital for normal striatal development and functional recovery.[28] Whole ganglionic grafts have produced better clinical and imaging data, and lack of vital components may explain the poor post-mortem findings where selectively-dissected LGE tissue was grafted.[17]

Processing
Once harvested, there is some evidence from both HD and PD transplant studies that grafts using cell suspension have better growth and connectivity with the host brain compared with solid transplants and are also less immunogenic.[11,28,30] One study that directly compared the two methods, but found little difference in terms of functional benefit in rodents.[29]

The amount of tissue transplanted may also be critical. For example, in the two UK studies the study that used three times the volume of tissue found long-lasting improvements in one patient[19] compared with the study that transplated a smaller tissue volume.[10]

Storage
The need to hibernate the harvested tissue is an obvious solution to the problem of tissue supply. Hibernation for up to eight days has been shown to have no adverse affect on grafted tissue.[31] Despite this, it is possible that the longer this period, the more likely it is that tissue may be compromised.[11]

Site of Engrafting
Whereas most studies distributed tissue evenly in the caudate and putamen, Hauser et al. targeted the post-commissural putamen known as the 'motor' striatum to help improve motor limb function.[14] A more even distribution of tissue over the whole striatum might be more logical, given the nature of HD, and may partly explain the disappointing findings of Hauser et al.[14] Gallina et al. used a novel stereotaxic procedure of double point entry to increase the number of tracks and spatial distribution of tissue across the striatal complex.[20] This may explain the post-operative reduction in choreic movements in two of their patients.[22]

Patient Numbers, Selection and Assessment
The outcome of the various trials shows that in order to assess efficacy it is vital to use consistent protocol and methods, such as the CAPIT-HD assessment protocol. However, even then the conclusions from small open-label studies, such as those considered here, should be cautionary as it is impossible to know what underlies any improvements. For example, constant monitoring and clinic visits alone may well have proved beneficial to patients.

The Future of Neural Transplantation
Despite a lack of long-term efficacy in many of the trials, the results are useful as they show that:

- neural transplantation is safe (at least in early-stage HD patients).
- transplantation does not adversely affect the course of HD and may even transiently slow it down;
- grafts can survive, although their ability to integrate into the host brain is not obvious; and
- grafts do not show signs of developing the disease in terms of intracellular protein aggregates.

Generally the majority of studies found a transient clinical improvement, but this does not seem to last for more than four to six years after the transplant. It is not certain exactly how the grafted tissue provides these benefits; imaging evidence of tissue survival suggests it may be due to direct cell replacement. Alternatively, the release of trophic factors by the graft, such as brain-derived neurotrophic factor, might support the growth of host cells and minimise or even prevent damage caused by the disease pathology,[22] all of which may be enhanced by the use of immunosuppressive drugs.

An issue that these transplant trials may be able to address is whether the extra-striatal atrophy that occurs in the brains of people with HD happens at the same time or later than striatal atrophy. If cortical and striatal atrophy occur concurrently, then replacing the striatum will be ineffectual. However, if striatal transplants prove effective this could be held as evidence for cortical degeneration occurring later, or at least in a way that is dependent in part on striatal atrophy.

In this respect, grafting of cortical tissue into the anterior cingulate cortex of transgenic HD mice resulted in a delay of rear paw clasping but no improvement in the motor rota-rod task.[32] This suggests that cortical transplants may also be effective, especially if used in combination with striatal grafts. Recent pathology, however, showed that the transplants may be affected by aberrant connections within the host brain. It also showed that part of the HD disease process involves the glial compartment and therefore may be important in driving the pathology in the graft.[17] As such, this approach would exacerbate graft pathology and reduce its clinical effectiveness.

Finally, there may be a role for environmental enrichment in treating patients. Both motor training and environment enrichment enhance the motor function of transplanted rodents, an effect that may well carry over into man, but has yet to be investigated further.[33,34]

Given some of the issues surrounding the use of foetal striatal tissue, it may be worth pursuing xenotransplantation. This would remove some of the ethical and logistical problems associated with the use of human foetal tissue, although it creates new issues, not least of which include rejection, retroviral infections and social stigma. One preliminary study that transplanted porcine foetal tissue in PD and HD patients presented little evidence for clinical improvement in HD patients and MRI scans failed to show graft survival. This is likely due to insufficient immunosuppression, an area that needs to be addressed before further xenotransplantation trials take place.[35]

Conclusion

A brief glimpse of the possibilities that neural transplantation with foetal striatal tissue could offer patients with HD has been provided in this article. Further work is needed to better understand the degenerative process at work in the HD brain, so it can be ensured the graft has as much chance of survival and integration as possible and eliminate the heterogeneity of results between and within patients. Of course, it may be that neural transplantation cannot work in the brains of patients with HD, or it may rely on combining transplants with neurotrophic factors or other technologies.

At this stage, it is clear that striatal foetal allografts may have some merit as a therapeutic option in patients with HD. Despite their merits, however, it is not clear how long these benefits last and whether they can truly alter the natural history of HD. ■

Roger A Barker is a University Reader in Clinical Neuroscience and an Honorary Consultant in Neurology at the Addenbrooke's Hospital, University of Cambridge. His main interests are in the neurodegenerative disorders of the nervous system, in particular Parkinson's and Huntington's disease. He combines basic research with clinically-based work on both of these conditions.

Rachel A Swain is a Research Assistant working at the Cambridge Centre for Brain Repair, University of Cambridge. Her work involves performing cognitive testing on patients with Huntington's and Parkinson's disease when they attend clinic. Her own studies involve investigating hippocampal function and decision-making in these patient groups.

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