Human Brain Grafting: An Approach to the Treatment of Neurodegenerative Diseases

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The aim of human brain grafting is to deliver adequate amounts of endocrine or neural tissue to neurodegenerated areas of the diseased or lesioned brain for functional recovery. The many options available make brain grafting and other neural grafting procedures potentially applicable for the treatment of varied alterations of the central nervous system, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis, spinal cord lesions, assorted traumatic lesions to the central nervous system, stroke, etc.

Over the last twelve years, great advancements have been made in the development of brain grafting for the treatment of PD.[1] With varying degrees of success, autologous adrenal medullary (AM) or human fetal ventral mesencephalon (VM) have been grafted to the striatum of PD patients using open microsurgery[2,3,4,5] or by stereotactic implantation.[6,7,8] The favorable outcome of a significant proportion of transplanted PD patients has not only led to the further development of PD brain grafting as a therapeutic alternative, but has encouraged us in particular to attempt the initial brain grafting trials for the treatment of HD using human fetal striatal (S) tissue.[9]

The neurosurgical treatment of PD by brain grafting has been especially well-suited as a starting point for the development of this procedure in humans. The characteristic motor disfunctions of PD mainly involve the neurodegeneration of a defined set of dopaminergic neurons of the pars

compacta of the substantia nigra (SN).[10] Initially, and for the first 8 to 10 years, the disease can be treated successfully with levodopa, which is taken up by the remaining viable neurons for the biosynthesis of dopamine (DA). Over the years, however, patients develop side effects that can be as disabling as the signs of the disease, or they can become less responsive to levodopa. Thus, replacing the degenerated dopaminergic neurons with DA-producing tissue could be a more promising treatment.

The clinical potential of DA-rich brain grafts for the treatment of PD was realized with the marked improvements seen in animal models (rats and non-human primates) of the disease after transplantation to the striatum of adult AM tissue, or fetal mesencephalic neurons.[11,12,13]

HD is an autosomal, fully dominant neurodegenerative disorder that results from the loss of function of gene IT15 in the short arm of chromosome 4.[14] Severe pathological changes in the caudate-putamen complex occur, which result in choreiform movements, cognitive decline, and personality disturbances. The disease is untreatable and progresses relentlessly to death.[15]

Experimental fetal S homotopic transplantations in animal models (rats and non-human primates) of the disease have been effective in restoring altered movement and behavioral functions.[16,17,18] Therefore the possibility exists that fetal striatal brain grafting in HD patients could retard the rate of their mental deterioration, and improve their overall functional capacity.[9]

The substance of the present work is based on our experience in human brain grafting for the treatment of PD and HD, using an open microsurgical approach. We have found this procedure to be adequate for the treatment of PD, using either AM tissue or human fetal VM, and are evaluating its usefulness for the treatment of HD using human fetal S tissue.

OPEN MICROSURGERY FOR BRAIN GRAFTING: AN ALTERNATIVE FOR THE TREATMENT OF PD AND HD

Open surgery is a widely used approach in neurosurgery. Using direct microscopic vision, it provides a safe and accurate access to almost any area of the central nervous system. Under controlled hemostasis, it allows for the direct visualization of the structure aimed as sole implantation site, or for multiple-site grafting, and allows for the recovery of biopsy specimens. Using open microsurgery, it is possible to achieve the rapid and accurate placement and attachment of living endocrine and neural tissue fragments with minimum manipulation to the graft and receptor brain. Reducing the time of exposure to anoxia and the amount of time the tissue is without nutrients should improve the quality and survival expectancy for the implanted graft. Also, the use of tissue blocks, instead of manipulated cell suspensions, could preserve as yet unidentified active elements of the graft.

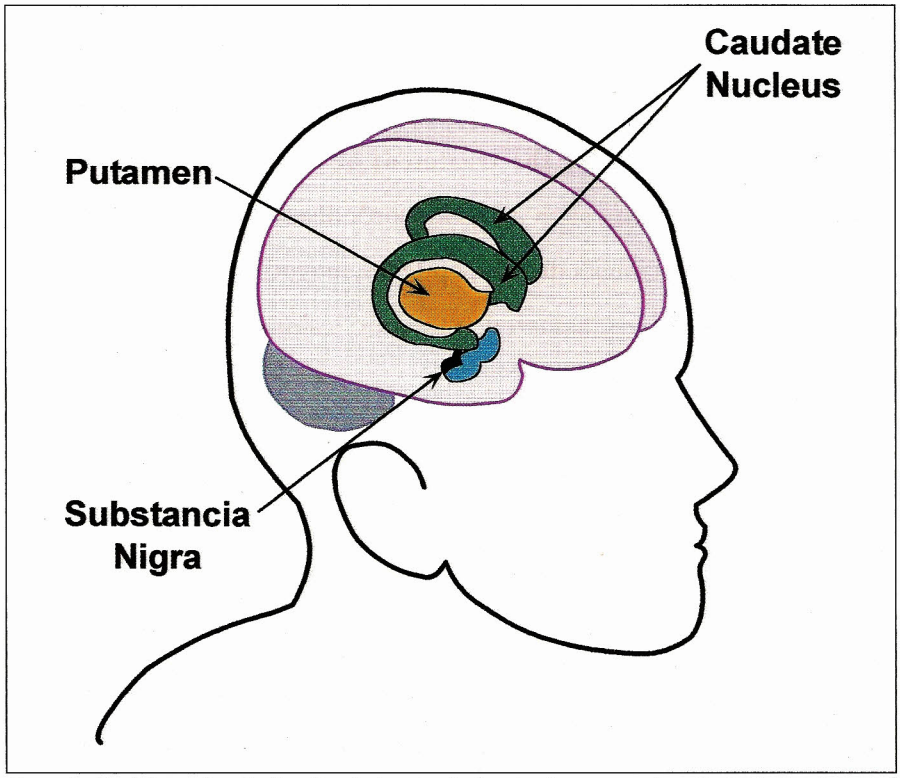

Figure 1. Caudate nucleus is the site of placement of endocrine or neural grafts in the treatment of PD or HD.

Surgical teams. For PD the successful transplantation of autologous AM tissue to the brain requires the precise coordination of 3 surgical teams: the neurosurgeons who implant the tissue, the general surgeons who remove the adrenal gland, and the team of surgeons who dissect the AM from the gland.

The transplantation of fetal VM for PD patients and of fetal S for HD patients requires the coordination between the team of neurosurgeons and the team of surgeons in charge of dissecting the fetal tissues, respectively.

Preparation and positioning of the patient. Patients are placed in the supine position, and their skull fixed with a pin head-holder in the primary position. For the autologus transplantation of AM tissue for PD, the head and abdominal areas are prepared with antiseptics simultaneously.

Anesthesia. Immediately prior to surgery, patients are given via I.V. 1 mg sulfate atropine, 10 mg diazepam, and 2 to 3 µg/kg citrate fentanyl. Anesthesia is induced with 2 to 5 mg/kg sodium thiopental, and neuromuscular relaxation is usually induced using 80 to 150 µg/kg pancuronium bromide. Endotracheal entubation is performed using a tube with a low-pressure balloon. This is followed by placement of a nasogastric tube, a bladder catheter, an atrial, and two peripheral I.V. catheters, as well as a radial arterial catheter. Throughout surgery patients are submitted to computerized monitoring of their vital signs, blood chemistry, and levels of O_2 and CO_2, and are kept on a mixture of O_2 (66%), N_2O (33%), and halothane (0.8 to 1.5%), enflurane (1 to 1.8%), or isoflurane (1 to 1.8%).

Craniotomy and transcortical ventricular placement of the grafts. The non-dominant brain hemisphere is chosen for surgery. A frontal U-shaped

skin incision (with a 6-cm diameter) is made immediately above the hair-line, and oriented toward the orbital region. A frontal 4 cm^2 craniotomy is performed, with 0.5 cm precoronal and 1 cm off the midline. The dura mater is opened in the cross-section.

A 3-mm bipolar coagulation is done in the pia mater in the posterior third of the second frontal gyrus (F2). A deflated double lumen balloon needle is introduced transcortically to the right frontal horn of the lateral ventricle, anteriorly to the foramen of Monro.[20] Approximately 20 ml of saline are introduced slowly into the balloon catheter for an atraumatic fiber dissection, producing a 1.5 to 2.0 cm diameter rounded tunnel access. The catheter is then replaced by two self-retaining retractors 1.0 cm wide, which are introduced into the ventricular cavity for the placement of the graft. The tip of the medial retractor is placed in such a way as to hold the corpus callosum, and then the lateral spatula is placed just over the head of the caudate nucleus (CN). Under the surgical microscope, the foramen of Monro, the choroid plexus, and the thalamostriatal vein are exposed. Once the CN has been clearly identified (Figure 1), one cavity or multiple cavities are made for the placement of the grafts in the ventricular wall of the head of the CN with pituitary forceps, in the avascular space between the caudate veins, to avoid bleeding.

Fetal material. Fetuses used for PD or HD brain grafting are of a gestational age of 9 to 14 weeks. Under Mexican law, fetuses can be obtained only after spontaneous abortions from mothers who test negative for hepatitis and HIV and who have no family history of HD. Immediately after fetal death diagnosis, the fetuses are transported to the neurosurgical unit on ice, and repeatedly cleansed with an ice-cold antiseptic solution. The dissecting procedures are performed on ice and under the dissecting microscope.

Immunosuppression therapy. Patients with fetal brain graftings are immunosuppressed. This therapy is started immediately prior to surgery with 10 mg/kg bw cyclorporine A given intravenously. After surgery, immunosuppression is sustained with cyclosporine A 10 mg/kg per day for 8 days, continuing with a descending program down to 5 mg/kg per day orally, and maintained indefinitely. Patients also receive prednisone 50 mg per day orally for 8 days post-surgery, continuing with a 6 month descending program to 5 mg per day. Steroid treatment is then discontinued.

Brain Grafting for PD. Three groups of PD patients received AM brain grafts in the head of the CN, using different transplantation strategies: patients (A-E) received the grafts in a single pre-cavitated site; in patients (F-J) the grafts were placed in multiple sites within the target area; while patients (K-N) were co-grafted with peripheral nerve tissue. The age, sex, years of evolution of PD, and post-surgery follow-up time for the three groups of PD patients are given in Table 1.

AUTOLOGOUS AM BRAIN GRAFTING FOR PD

Adrenalectomy. A left subcostal laparotomy is made from the midline to the anterior axillary line. The adrenal gland is exposed. The gland is usually situated on the higher pole of the kidney near the spine and is differentiated from the capsule of the kidney by its consistency and color. It is important to stress that the pancreas should be managed with extreme care to avoid post-surgical complications. Once it has been clearly identified, the adrenal gland is carefully dissected. The adrenal vein is exposed, clamped, clipped, and severed.

Adrenal gland dissection. Placed on a cold plate and irrigated with iced saline, the gland is cut transversely in two halves, and each half is then divided longitudinally. Under the surgical microscope the AM tissue can be identified as a soft white-grayish structure. The usual amount of tissue available in PD patients ranges between 0.4 and 1 g. The medullary tissue is fragmented into 6 to 8 portions and delivered to the neurosurgeon on wet surgical cottonoid strips. This procedure should take no longer than 15 minutes.

AM brain grafting. AM grafts are placed unilaterally in one pre-cavitated site in the CN, and then fixed in place with titanium clips.

Summary of Clinical Data and Current Condition of AM Brain Grafted PD Patients

Patients	Sex/ Age•(y)/ PD evol•(y)	Follow-up time (mo)	Current PD Condition••
	Unisite AM Brain Grafts		
A	M/33/10	65	unchanged
B	M/34/3	64	unchanged
C	F/42/15	65	moderately improved
D	F/35/8	63	unchanged
E	M/58/10	62	moderately improved
	Multiple Site AM Brain Grafts		
F	M/37/9	48	unchanged
G	M/41/4	48	unchanged
H	M/52/12	44	moderately improved
I	F/51/22	36	unchanged
J	M/53/8	32	unchanged
	AM Brain Grafts Cografted with PNT		
K	M/43/8	31	improved
L	M/48/10	35	moderately improved
M	F/51/13	26	unchanged
N	M/41/5	25	unchanged

At the time of surgery. •• As compared to each patient's preoperative PD condition. AM: adrenal medullary; PD: Parkinson's disease; PNT: peripheral nerve tissue; M: male; F: female; y: years; mo: months.

Table 1.

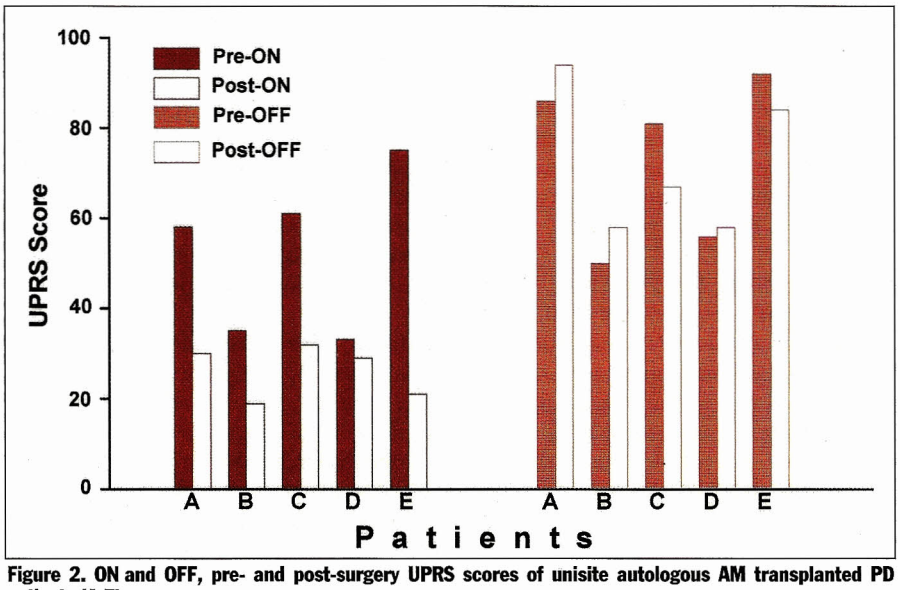

Figure 2. ON and OFF, pre- and post-surgery UPRS scores of unisite autologous AM transplanted PD patients (A-E).

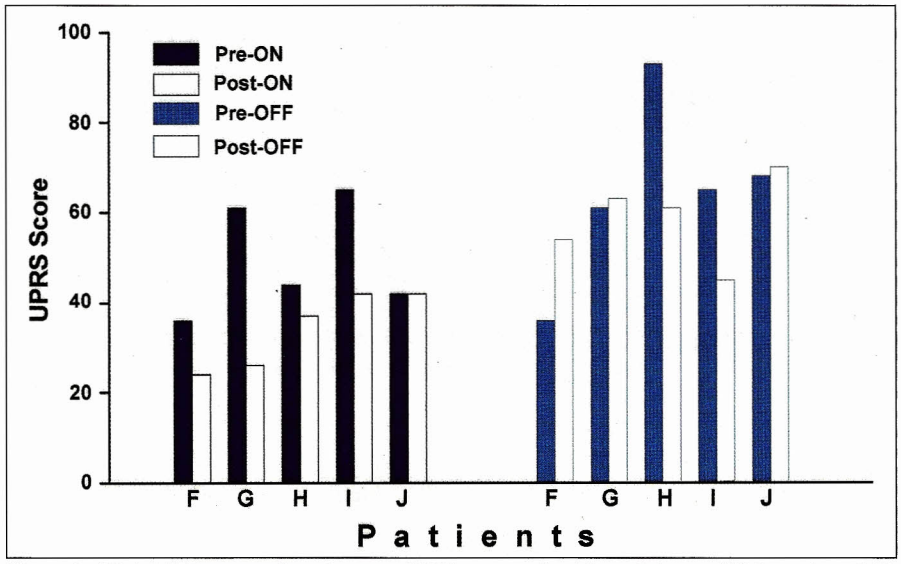

Figure 3. ON and OFF, pre- and post-surgery UPRS scores of unisite autologous AM transplanted PD patients (F-J).

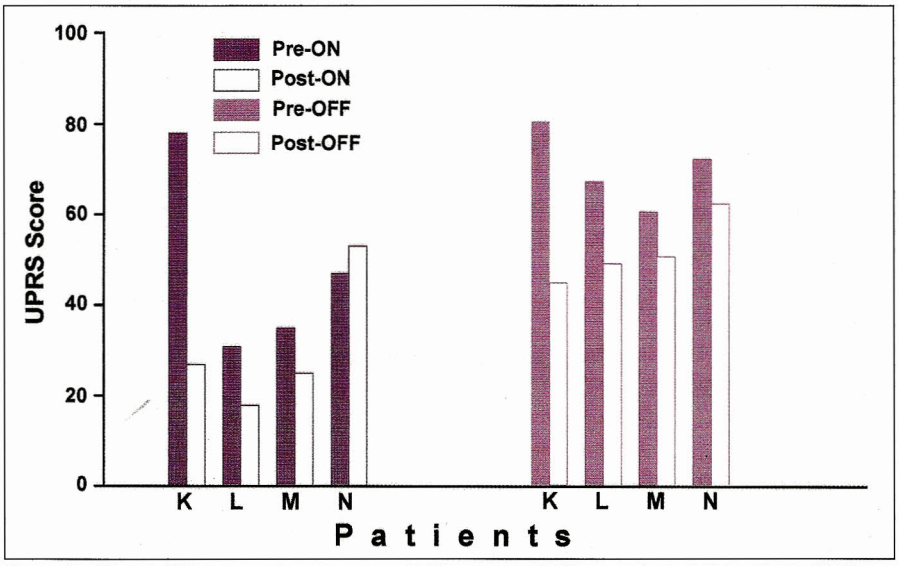

Figure 4. ON and OFF, pre- and post-surgery UPRS scores of AM transplanted PD patients (K-N) co-grafted with peripheral nerve tissue.

Alternate strategies for AM brain grafting. Variations to the original transplantation procedure have included co-grafting AM tissue with autologous peripheral nerves, with the purpose of promoting neurogenization of the chromaffin cells and enhancing trophism, or placing the AM fragments in multiple sites in the head of the CN, without precavitation, in order to increase contact surface and extend dopaminergic activity to a greater area within the diseased striatum.

Neurologic evaluations for PD. The neurologic condition of all AM and VM transplanted PD patients is evaluated in the ON (with medication, levodopa) and the OFF conditions (without levodopa), before and after surgery on the Unifed Parkinsonism Rating Scale (UPRS),[20] the Schwab and England (SE),[21] and the Hoehn and Yahr (HY)[22] rating scales. Only their UPRS scores are presented here.

Clinical outcome after AM brain grafting. Figures 2 through 4 depict the 4- to 5-year and 2- to 3-year post-surgical neurologic evaluations on the UPRS of AM grafted PD patients of:

- 5 patients (A-E) in whom the AM grafts were placed in a single cavitated site in the CN (Figure 2),
- 5 patients (F-J) with AM grafts to multiple sites in the CN without pre-cavitation (Figure 3), and
- 4 patients (K-N) with AM cografted with peripheral nerve tissue to a single pre-cavitated site in the CN (Figure 4).

After 62 to 65 months post-surgery, PD patients with unisite AM brain grafts show improved response in the post-ON condition (in the presence of levodopa medication); patients with AM co-grafted with peripheral nerve tissue reveal an improved post-OFF condition 25 to 35 months post-surgery, which suggests an improvement in their basal PD condition, while 32 to 48 months post-surgery patients with multiple-site AM grafts do not reveal a uniform response to the surgical intervention.

Fetal VM brain grafting for PD. Four PD patients (O-R) received human fetal VM grafts to the CN. Their clinical data are shown in Table 2.

Fetal VM dissection. The skin and skull are coronally cut open with scissors. The cerebral hemispheres are removed, carefully preserving the thalamus. After bilaterally severing the tentorium, the brain stem is retracted, and the cranial nerves cut. Upon visualizing the foramen magnum, the junction at the medulla oblongata and spinal cord is severed, freeing the entire brain stem and thalamus as one block and is placed on a wet cottonoid strip. The cephalic flexure and the various parts of the brain stem are identified allowing to coronally slice out the mesencephalon. The mesencephalic coronal slice is placed on its rostral side and the peduncles, tectum, and medial aspect are removed. The remaining untouched blocks of tissue are the VM used for human brain grafting. This procedure should last no longer than 15 minutes. The time elapsed between fetal death diagnosis and implantation should be no longer than 3 hours.

Fetal VM brain grafting. The neurosurgical technique used is the same as that described above for AM brain grafting. Fetal tissue is embedded into one site of the ventricular wall of the head of the CN and fixed with titanium clips. A patient's pre- and post-surgical neurological condition is recorded on the SE, HY, and UPRS. Only the UPRS scores are presented.

Clinical outcome after fetal VM brain grafting. At their neurological evaluations 44 to 58 months post-surgery, PD patients (O-R) with fetal VM grafts show improvements in their UPRS scores both in ON and OFF (Figure 5), thus reflecting an improved response to levodopa and suggesting an improvement in their basal PD condition.

Brain Grafting for HD

Unilateral fetal S implantations to the CN were performed in two Mexican HD patients. Their clinical data are summarized in Table 3. Case 1 inherited the disease from her father and at the time of surgery her condition was rated as moderate to severe. Her surgery was performed on November 2, 1990. Case 2 inherited the disease from his mother. At the time of surgery his condition was rated as mild. His surgery was performed on June 25, 1992.

Fetal S brain grafting for HD

Fetal S dissection. This procedure is a simple and rapid enucleation technique for the removal of both fetal striata, with minimum manipulation to this tissue; it was designed to be completed within 15 minutes.

Fetal S brain grafting. The neurosurgical technique used is the same as that described above for fetal VM brain grafting. Fetal tissue is embedded into 4 precavitated sites in the ventricular wall of the head of the CN. Grafts are not fixed with clips. Patients are

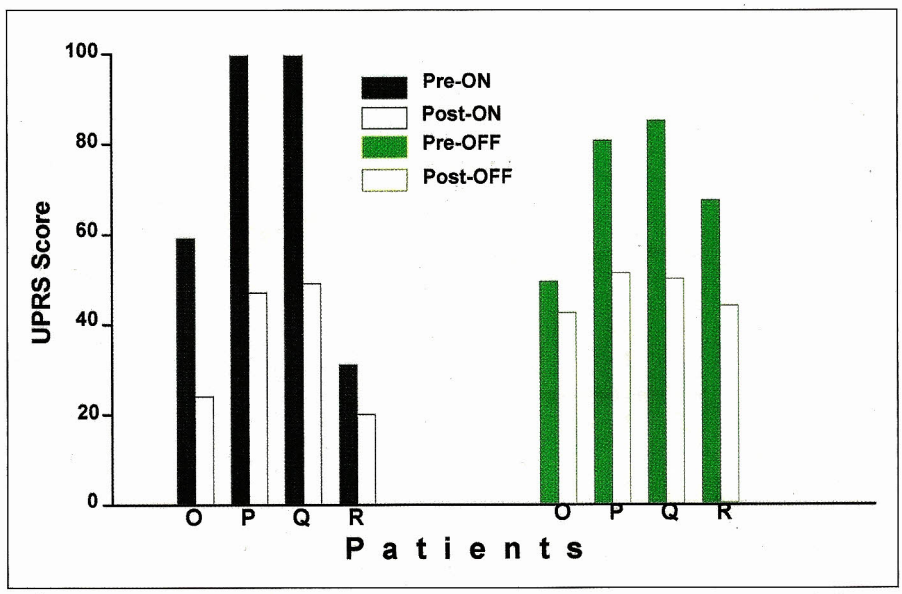

Figure 5. ON and OFF, pre- and post-surgery UPRS scores of fetal VM transplanted PD patients (O-R).

Summary of Clinical Data and Current Condition of Fetal VM Brain Grafted PD Patients

Patients	Sex/ Age•(y)/ PD evol•(y)	Follow-up time (mo)	Current HD Condition••
O	M/50/9	58	moderately improved
P	M/45/16	50	improved
Q	M/52/13	49	improved
R	M/47/9	45	unchanged

At the time of surgery. As compared to each patient's preoperative PD condition. PD: Parkinsion's disease; VM: ventral mesencephalon; M: male; y: years; mo: months.

Table 2.

Summary of Clinical Data and Current Conditions of Fetal Striatal Brain Grafted HD Patients

Patients	Sex/ Age•(y)/ HD evol•(y)	Follow-up time (mo)	Current HD Condition••
1	F/37/9	41	deteriorated
2	M/29/4	23	deteriorated

•At the time of surgery. ••As compared to each patient's preoperative condition.
HD: Huntington's disease; F: female; M: male; y: tears; mo: months.

Table 3.

immunosuppressed with cyclosporine A. Surgery produces no adverse side effects.

Neurologic evaluations for HD. The patients' HD condition before and after surgery is rated on the following HD scales: the abnormal involuntary movements scale (AIMS); the Marsden and Quinn rating scale (MQ); the Shoulson and Fahn rating scale (SF); and the disability rating scale (Dis).[23]

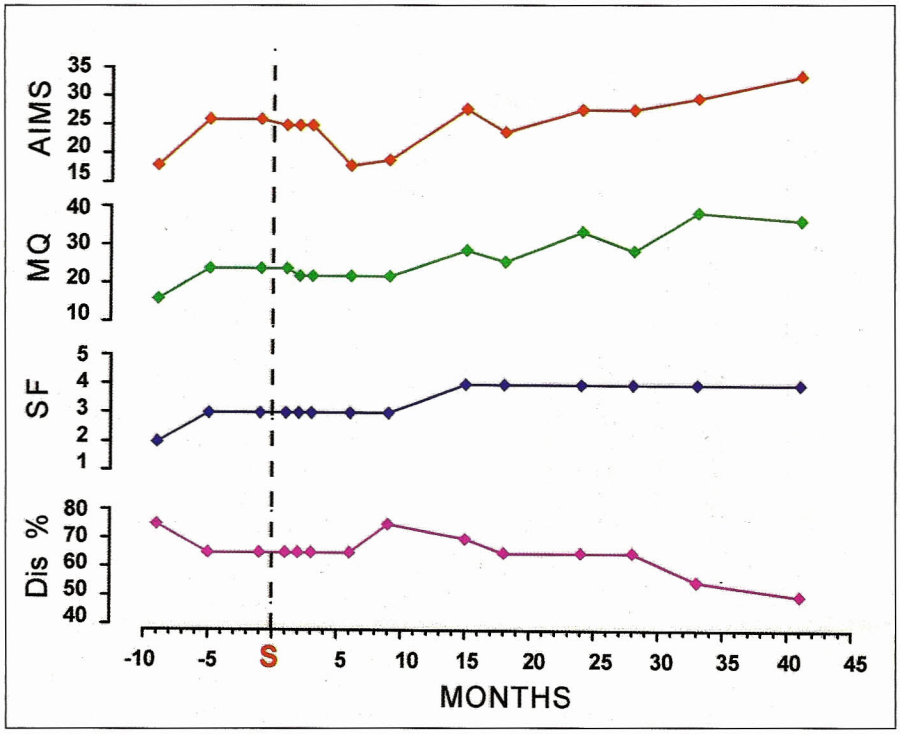

Figure 6. Pre- and post-surgery time course of evolution of HD for case 1 on the abnormal involuntary movements scale (AIMS), the Marsden and Quinn scale (MQ), the Shoulson and Fahn scale (SF), and the disability scale (Dis).

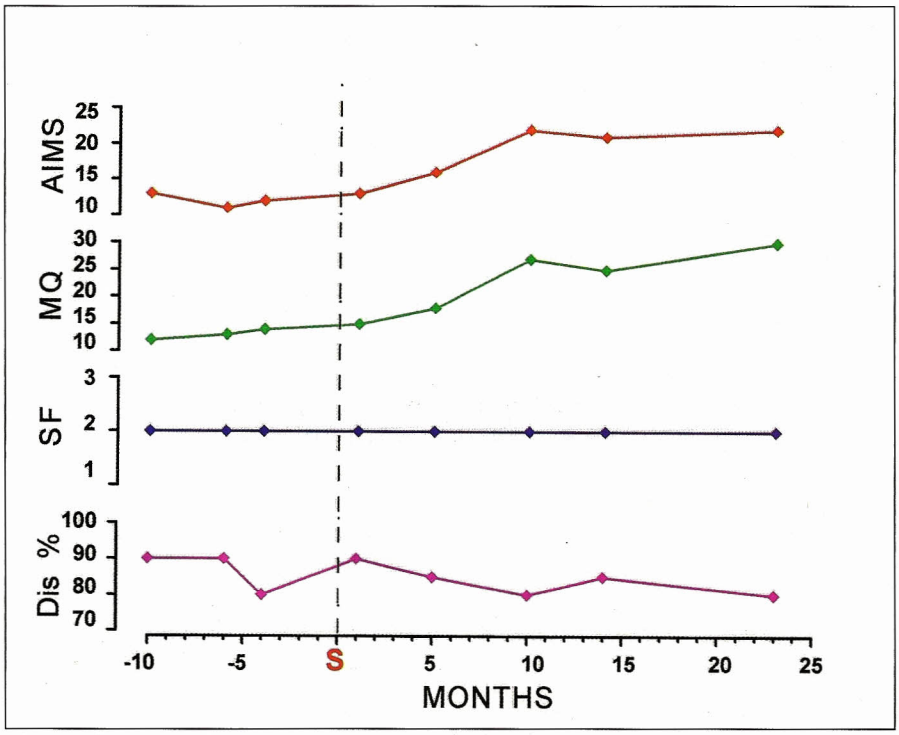

Figure 7. Pre- and post-surgery time course of evolution of HD for case 2 on the abnormal involuntary movements scale (AIMS), the Marsden and Quinn scale (MQ), the Shoulson and Fahn scale (SF), and the disability scale (Dis).

Clinical outcome after S brain grafting. The time course of the neurological evolution for the HD cases 1 and 2, before and after surgery are depicted on all four HD scales in Figures 6 and 7, respectively. The surgical intervention had no acute damaging effect on either patient. After showing minor signs of transitory improvement, it is apparent that surgery did not inhibit the progression of the disease, although its impact on the rate of progression of the disease remains unclear.

CONCLUSIONS

The purpose of human brain grafting is to attempt to replace a lost neural function with endocrine or neural tissue, as sources of lost neurotransmitters, neurotrophic factors, or other neural elements missing in the diseased brain. Although there are many groups worldwide devoted to the development of human brain grafting as a therapy for the treatment of PD and HD diseases, the procedure is still in its infancy. Fundamental issues that have still not been decided upon, and are under active experimentation, include:

- establishing which patients are the best candidates for surgery; that is, those PD or HD patients most likely to benefit from brain grafting;
- determining the amount of tissue necessary to significantly improve lost neuronal function and ameliorate signs and symptoms of the disease or at least arrest their progression;
- establishing the preference to use neural tissue fragments instead of cell suspensions for grafting to ensure the inclusion of factors that might be lost during the preparation of cell suspensions;
- determining if there is a real risk of rejection of fetal tissue after brain transplantation that warrants immunosuppression;
- establishing the optimum gestational age of the donor fetus;
- determining the requirement of bilateral instead of unilateral brain grafting;
- establishing the best area or areas in the brains of PD or HD patients for tissue grafting;
- determining if the graft will become a target of the disease process in the brains of PD or HD patients;

- establishing the most adequate means of assessing the effect of the brain grafts on the disease process in afflicted individuals.

An open interaction among the various clinical and basic research groups in this field will surely hasten our arrival to a fully developed and versatile neural-grafting technology for multiple diseases and lesions that affect the central nervous system. STI

REFERENCES

1. Madrazo I, Franco-Bourland R, Aguilera M, Ostrosky-Solís F, Cuevas C, Castrejón H, Magallón E, Madrazo M. Development of human neural transplantation. Neurosurgery 1991; 29:165-177.
2. Madrazo I, Drucker-Colín R, Díaz V, Martínez-Mata J, Torres C, Becerril JJ. Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. N Engl J Med 1987; 316:831-834.
3. Goetz CG, Olanow CW, Koller WC, Penn RD, Cahill D, Morantz R, Stebbins G, Tanner CM, Klawans HL, Shannon KM, Comella CL, Witt T, Cox C, Waxman M, Gauger L. Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. N Engl J Med 1989; 320:337-341.
4. Madrazo I, Franco-Bourland R, Ostrosky-Solís F, Aguilera M, Cuevas C, Zamorano C, Morelos A, Magallón E, Guízar-Sahagún G. Fetal homotransplants (ventral mesencephalon and adrenal tissue) to the striatum of parkinsonians. Arch Neurol 1990; 47:1281-1285.
5. Madrazo I, Franco-Bourland R, Aguilera M, Madrazo M, Dector T. Transplantation techniques. Open microsurgery for human brain transplantation: experience in the treatment of Parkinson's disease. In: Lindvall O, Björklund A, Widner H (Eds.). Intracerebral Transplantation in Movement Disorders. Elsevier, Amsterdam, 1991; 153-162.
6. Jiao S, Ding Y, Zhang W, Cao J, Zhang Z, Zhang Y, Ding M, Zhang Z, Meng J. Adrenal medullary autografts in patients with Parkinson's disease. N Engl J Med 1989; 321:324-325.
7. Lindvall O, Brundin P, Widner H, Rehncrona S, Gustavii B, Frackowiak R, Leenders K, Sawle G, Rothwell J, Marsden CD, Björklund A. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 1990; 247:574-577.
8. Apuzzo MLJ, Neal JH, Waters CH, Appley AJ, Boyd SD, Couldwell WT, Wheelock VH, Weiner LP. Utilization of unilateral and bilateral stereotactically placed adrenomedullay-striatal autografts in parkinsonian humans: rationale, techniques, and observations. Neurosurgery 1990; 26:746-757.
9. Madrazo I, Franco-Bourland R, Castrejón H, Cuevas C, Ostrosky-Solís F, Aguilera M, Magallón E, Velázquez D, Guíza-Sahagún G, Grijalva I, Zamorano C. Fetal striatal homotransplantation for Huntington's disease: report of the first two clinical trials. Neurol Res (in press).
10. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and syndromes of Parkinson's and Huntington's disease. J Neurol Sci 1975; 30:415-455.
11. Olson L, Strömberg I, Herrera-Marschitz M, Ungerstedt U, Ebendal T. Adrenal medullary tissue grafted to the dopamine-denervated rat striatum: histochemical and functional effects of additions of nerve growth factor. In: Björklund A, Stenevi U (Eds.). Neural Grafting in the Mammalian CNS. Elsevier, Amsterdam, 1985; 505-518.
12. Dunnett SB, Björklund A, Gage FH, Stenevi U. Transplantation of mesencephalic dopamine neurons to the striatum of adult rats. In: Björklund A, Stenevi U (Eds.). Neural Grafting in the Mammalian CNS. Elsevier, Amsterdam, 1985; 451-469.
13. Bankiewicz KS, Plunkett RJ, Jacobowitz DM, Porrino L, Di Porzio U, London WT, Kopin IJ, Oldfield EH. The effect of fetal mesencephalon implants on primate MPTP-induced parkinsonism, histochemical and behavioral studies. J Neurosurg 1990, 72:231-244.
14. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993; 72:971-983.
15. Martin JB, Gusella JF. Huntington's disease. Pathogenesis and management. N Engl J Med 1986; 315:1267-1276.
16. Isacson O, Brundin P, Gage FH, Björklund A. Neural grafting in a rat model of Huntington's disease: progressive neurochemical changes after neostriatal ibotenate lesions and striatal tissue grafting. Neuroscience 1985; 16:799-817.
17. Isacson O, Dunnett SB, Björklund A. Graft-induced behavioral recovery in an animal model of Huntington's disease. Proc Natl Acad Sci USA 1986; 83:2728-2732
18. Hantraye P, Riche D, Maziere M, Isacson O. Intrastriatal transplantation of cross-species fetal striatal cells reduces abnormal movements in a primate model of Huntington's disease. Proc Natl Acad Sci USA 1992; 89:4187-4191.
19. Madrazo I, Franco-Bourland R, Aguilera MC, Reyes P, Guízar-Sahagún G. Balloon needle for the atraumatic transcortical ventricular approach: technical note. Surg Neurol 1990; 33:226-227.
20. Koller WC. Handbook of Parkinson's Disease. Marcel Dekker, New York, 1987.
21. Schwab RS, England AC Jr. Projection technique for evaluating surgery in Parkinson's. In: Gillingham FJ, Donaldson IML (Eds.). Third Symposium on Parkinson's Disease. E & S Livingstone, Edinburgh, 1968; 152-157.
22. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967; 17:427-442.
23. Weiner WJ, Lang AE (Eds.) Movement Disorders. A Comprehensive Survey. Appendix: Rating Scales for Movement Disorders. Futura, New York, 1989; 685-724.