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Clinical experience with cotransplantation of peripheral nerve and adrenal medulla in patients with Parkinson's disease

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Abstract Coimplants of adrenal medulla (AM) and peripheral nerve (PN) in animal models of Parkinson's disease (PD) have shown that AM cells survive longer, tend to show neuronal phenotype, and enhance sprouting of host fibers. Since 1987, our implants of perfused AM and fetal ventral mesencephalon (FVM) in PD patients have achieved varying degrees of clinical improvement. If the donor tissue determines the improvement, different types of implants should result in qualitatively and quantitatively different degrees of improvement. The purpose of this study is to determine whether or not the clinical course, improvement slope, and reduction of medication observed in PD patients who undergo tissue transplantation (Tx) depend on the donor tissue type. In a pilot study, four grade IV–V PD patients received implants of precoincubated autologous AM and intercostal nerve in the caudate nucleus (open surgery). Clinical assessment was based on international scales (UPD) as reported for Tx of FVM and perfused AM. There were no systemic or neurologic complications. Four years post-Tx, longer On phases and improved PD symptoms (ADL and motor-UPD) in On and Off persist in four cases, with reduced dyskinesias. Progress appears to be stepwise, starting within weeks of Tx (similar to AM and sooner than our FVM implants), followed by a period of stability and, after a second wave of improvement 12–18 months post-Tx (similar to FVM implants), continues to date. L-dopa medication has been reduced by more than 60 % and dopamine agonist use has not resumed. We conclude that our recipients continue to be clinically better than prior to Tx. The course of recovery after co-Tx of AM and PN differs from that of FVM or AM implants. This fact may be related to the etiological factors that produce the improvement.

Key words Parkinson's disease · Grafts · Dopamine · Adrenal medulla · Neurotrophic

Introduction

In view of the results obtained in animal models involving substantia nigra or adrenal medulla transplants, together with the fact that many parkinsonian patients do not respond to medication, Parkinson's disease has, in recent years, become one of the most widely studied neurological disorders by workers in the field of neural transplants. Clinical trials with adrenal medulla and embryonic tissue have been carried out in several research centers around the world, especially in Europe and America [for review see 8, 17, 18, 30]. The reported clinical results have not been homogeneous, ranging from minor or non-significant clinical changes to moderate or marked alleviation of the motor symptoms, generally accompanied by a greater or lesser reduction in the

L-dopa intake. In most cases, the published results have been more modest than expected.

In 1987, we undertook a controlled study to determine whether the implantation of neural tissue into an open cavity in the caudate nucleus was capable of producing an improvement in severely affected parkinsonian patients, and whether this improvement depended on the type of tissue implanted or was the consequence of surgical trauma and the implantation site. The results obtained in the first two series of graft recipients have shown that the implantation of perfused adrenal medulla [21, 22] or fetal ventral mesencephalon [23, 25] into the caudate nucleus by open surgery can improve the clinical symptomatology of severely impaired parkinsonian patients, and that this recovery is accompanied by a reduction in the L-dopa intake of more than 50 %. However, the duration of the clinical improvement observed and the moment of onset differ depending on the tissue implanted; that observed with fetal tissue graft occurred later and lasted longer than that resulting from implantation of adrenal medulla which occurred earlier and followed a stormier course.

As a continuation of our research into the relationship between the type of tissue implanted and the clinical improvement observed, we present our third series of patients. This report describes the overall clinical course of four grade IV–V Parkinson's disease patients 3 years after coimplantation of adrenal medulla and peripheral nerve (AM+PN) into the caudate nucleus. The incubation and implantation of peripheral nerve together with the adrenal medulla is justified by animal experiments showing that coimplants of adrenal medulla and peripheral nerve or implantation of adrenal medulla plus chronic nerve growth factor infusion increases the survival of the chromaffin cells of the adrenal medulla, favors the tendency of these cells to be of neuronal phenotype, and enhances the sprouting of host fibers [4–6, 14, 31].

Patients and methods

Between May and July of 1990, four parkinsonian patients in our center received coimplants of autologous adrenal medulla and intercostal nerve. The patients consented to participate in the study after being informed of the clinical and surgical risks, the possible lack of improvement, and the fact that the study focused more on clinical research than on the therapeutic measure. The use of the donor tissue and the experimental procedure were approved by the human research ethics committees of the center, with the consent of the Spanish National Institute of Health, and followed the guidelines of the pertinant Spanish law.

Patient selection and preoperative clinical features

The selection criteria for the patients were those used in our previous series of recipients of perfused adrenal medulla [21, 22] or fetal ventral mesencephalon [23, 25] transplanted into the caudate nucleus: parkinsonian patients in an advanced stage of the disease, with a history of Parkinson's disease of several years' duration, with no pharmaceutical control, and who presented normal daily fluctuations and dyskinesias. All the patients had responded to L-dopa administration at the onset of their disease. The mean age at surgery was 60 ± 6.78 years (range 52–67 years), the mean duration of their disease course was 10.87 ± 1.75 years (range 9–13 years), and they had been receiving L-dopa/inhibitor for 10.25 ± 1.26 years (range 9–12 years). They had participated in other clinicopharmaceutical trials with no appreciable control of their symptomatology. All the patients had received dopaminergic agonists. Disease severity ranged between grades IV and V of the Hoehn-Yahr scale, with one grade IV patient and three in grade IV–V.

Evaluation of the patients (clinical monitoring)

The subjects were assessed pre- and postoperatively, during On and Off stages under their usual medication and during predefined Off and On periods, and their status was determined on the basis of internationally accepted rating scales (CAPIT protocol) [16]. Predefined Off was considered to be the clinical situation of a patient examined between 10 and 11 am, 2–2.5 h after waking, before breakfast and 12–14 h after the last L-dopa dose. Predefined On was established as the clinical situation of a patient at the time of maximal therapeutic benefit, 1–1.5 h after the first regular morning L-dopa dose. Patient disability was classified as Hoehn-Yahr stages I–V on the basis of the Hoehn-Yahr scale. Motor function and normal daily activities were rated according to the Unified Parkinson's Disease Scale (UPDS, v. 3.0.1) and the North Western University Disability Scale (NWDS). Magnetic resonance imaging of the brain was performed prior to surgery and 1, 6 and 12 months after.

Pharmaceutical management

As in our first two series of implant recipients, the subjects of this trial were maintained on optimal doses of medication (L-dopa, agonists, and anticholinergics) until 1–2 weeks before surgery, at which time the dopaminergic agonists and/or amantadine were gradually tapered off, to be discontinued 1 day before implantation. Immediately after surgery, all the patients received dexamethasone (4 mg four times daily) and phenytoin at the standard postoperative dose. In this series of patients, it was also necessary to reduce L-dopa intake during the initial postoperative weeks, due mainly to motor complications. During the period of analysis (3 years), the dose was reduced whenever an increase in the dyskinesias or onset of psychiatric symptoms was observed.

Surgical procedure

The methods employed in the implantation procedure did not differ from those used for perfused adrenal medulla implants [21, 22], with the exception of the procurement and dissection of a peripheral nerve and its incubation with the pieces of adrenal medulla. The right adrenal gland was removed retroperitoneally using a superior subcostal approach. The gland was cut into slices about

5 mm thick and the adrenal medulla was dissected and incubated first in calcium- and magnesium-free buffer, and later in minimum essential medium (MEM), as previously described [19]. The viability of the chromaffin cells was over 70 %. The 12th intercostal nerve was dissected, freed of fat and the surrounding connective tissue, and then minced and incubated with the adrenal medulla in enriched Dulbecco's modified Eagle medium (DMEM) for approximately 1 h. The time between tissue preparation and implantation was less than 3 h. The donor tissue (a cohesive mass made up of 15–20 pieces of adrenal medulla and peripheral nerve measuring 2–3 mm each) was implanted into a cavity created in the right caudate nucleus (in direct contact with the cerebrospinal fluid of the lateral ventricle) after right frontal cariectomy and a transcortical (F2) approach to the lateral ventricle. The tissue was secured within the cavity with Surgical and clips.

Statistical study

The means and standard deviations of the clinical values were determined and the changes occurring over the entire course of the study were compared using non-parametric analysis of variance (Friedman's test) and Wilcoxon's paired test.

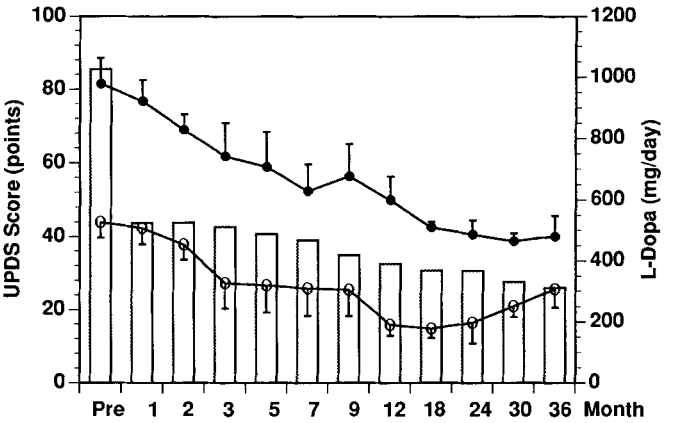

Fig. 1 Overall progress in the parkinsonian symptomatology from presurgery to 36 months postsurgery, assessed according to the Unified Parkinson's Disability Scale (UPDS), during practically defined Off and On periods as compared to L-dopa/inhibitor treatment course. Values are mean scores ± SD. Presurgery values represent the means ± SD of the evaluation performed over the 6 months prior to implantation

Results

Postoperative course, clinical symptoms, and medication

Thirty-six months after implantation, all four patients presented a sustained improvement in their parkinsonian symptomatology in On and Off (Fig. 1) and an increment in the percentage of their waking hours spent in On phase (Table 1), with decreased duration and reduced intensity of dyskinesias (Table 2). The improvement or increment in the number of waking hours spent in On appears to commence in month 2 and progresses steadily thereafter until the end of the follow-up (36 months after surgery). At the same time, the increase in time spent in On is accompanied by a reduction in the L-dopa administered; thus, not only did the patients spend most of the day in On stage, but they also took 69.5 % less medication (Table 3). Moreover, the quality of the time the patients spent in On was better (with respect to both routine daily activities and social life), since the improvement in motor function in the patients was also accompanied by a marked reduction in the duration (75 % less) and intensity of the dyskinesias (Table 2). The most notable decrease in the time spent with dyskinesias in On appeared to commence in months 2 to 3 when a reduction was observed in all four patients. At the end of the follow-up, the four patients had reduced the amount of On time spent with dyskinesias by 100 % to 54.5 % of the preoperative values.

Figure 1 shows the overall clinical course of the symptoms in predefined On and Off phases from the preoperative period to 36 months after implantation. As shown, the improvement in the clinical symptoms in Off followed two separate waves, one commencing in the first month of follow-up and persisting until months 7–9, and the second occurring 12–18 months postsurgery, with progression until the end of the follow-up period. In the initial postoperative weeks, as in our other implant series [21–23, 25], there was a slight deterioration in the symptoms, probably as a consequence of the withdrawal of dopamine agonists and the reduction in medication secondary to the onset of the motor and psychiatric complications. The clinical improvement involved all the symptoms analyzed in Off phase, although the degree and period of onset varied for each one (Table 4) and differed from those observed in the group of patients who received fetal tissue implants [25]. Facies and rigidity were the symptoms associated with the earliest (1 month after surgery) and the most notable recovery in the four patients, while postural stability, gait, and body bradykinesia improved later (5th month) and to a slightly lesser degree. Tremor was was the symptom that presented the least recovery.

Complications

There were no apparent systemic or general neurologic complications, but three of the four patients presented psychiatric complications in the form of personality changes (in one patient), confusion (in two), hallucinations (in three), delusions (in one), and vivid dreams (in two), while dyskinesias increased in all the recipients. From the experience gained in the first two series of patients [21–23, 25], L-dopa/inhibitor was gradually reduced from 1025 ± 210.59 mg/day presurgery to 525 ± 178.78 mg/day by the second month; this reduc-

Table 1 Mean percentage waking hours spent in On/day from month 1 to 36 months after surgery, as compared to mean percentage presurgery On time

Time of assessment	Percentage time spent in On/day
Presurgery	46.2 ± 10.4
Months after surgery	
2	63.75 ± 14.88
7	71.06 ± 10.90
18	73.21 ± 12.44
24	76.84 ± 7.78
36	87.5 ± 10.4

Table 2 Mean percentage On time spent with dyskinesias ± SD from 1 to 36 months after surgery as compared to mean percentage presurgery On time with dyskinesias

Time of assessment	% On time with dyskinesias
Presurgery	67.10 ± 9.18
Months after surgery	
2	45.11 ± 13.05
3	18.72 ± 37.63
9	10.55 ± 9.08
12	11.0 ± 10.36
24	15.9 ± 7.0
36	17.08 ± 13.76

Table 3 Mean L-dopa/carbidopa dose from 1 to 36 months after surgery as compared to mean presurgery dose

Time of assessment	L-dopa/inhibitor (mg/day)
Presurgery	1025.00 ± 210.59
Months after surgery	
2	525.00 ± 170.78
7	468.75 ± 177.12
12	391.25 ± 320.16
18	368.75 ± 189.66
24	368.75 ± 124.79
30	331.25 ± 87.50
36	312.50 ± 180.97

tion was associated with an improvement in the motor complications and the disappearance of hallucinations and delusions.

Discussion

The results of this pilot study demonstrate that parkinsonian patients improve after the cografting of AM + PN implants. This recovery changes the daily living activities of the patients, allowing them to perform routine activities with increasing ease. This improvement is evident in the decrease in severity of all the parkinsonian symptoms, although to different degrees and with different rates of onset. To the physicians that have been following these patients for years, the reduction in the dosage of medication (L-dopa), the parallel increase in the length of time throughout the day in which the patient is in On, with alleviation of the secondary motor complications (mainly dyskinesias) and the lowering of the disease grade is suggestive of a return to an earlier and more benign stage of the disease, as though time had been turned back.

As we have mentioned in earlier publications, the difference in the study design makes it difficult to compare our results with those of other groups, whether they employed stereotactic techniques [1, 2, 9, 11, 13] or open surgery [26, 27]. If in the former case, the main differences lie in the implantation site and the surgical technique employed, in the latter which is more comparable given the similarity in the surgical technique, they lie in the type of patients undergoing implantation (younger and with a shorter history of chronic medication), in the clinical follow-up, and in the fact that none of the research teams has performed implantation using adrenal medulla and peripheral nerve as donor tissue.

Having arrived at this point, the reader may ask how can it be that the results of so many of the studies documented in the literature show the improvement of implant recipients when these reports generally disagree with respect to the site of implantation (caudate or putamen or both), the type of tissue (adrenal medulla or fetal tissue), the amount of tissue implanted (tissue from one or more fetuses), the severity of the disease in the implant recipients (grade III–V), and the protocol for clinical follow-up. Reading these articles creates the impression that some degree of improvement can be obtained in transplant recipients regardless of the donor tissue employed. From our point of view, this consideration is misleading. A critical reader of this article who is familiar with our work may arrive at the conclusion that, in the paradigma employed by us, consisting of "implantation, using an open surgery technique, of tissue grafts from different sources into the caudate nucleus of severely disabled parkinsonian patients", the patients in each study series (perfused adrenal medulla, fetal tissue, and AM + PN coimplants) [20–25] improve postoperatively and return to a certain degree of disability, regardless of the tissue implanted. In agreement with this rationale, the response would be that the recipients of implants in the caudate nucleus do indeed improve regardless of the tissue employed. However, the degree of recovery and its time of onset and clinical course are different for each tissue type. In implants of perfused adrenal medulla [20–22], the improvement has an early but stormy commencement, starting in the first month and progressing stepwise until months 9–12. From then on, the gains stabilize in most of the patients, with no further progress. In contrast, when fetal ventral mesencephalon is implanted, the onset of clinical recovery and the improvement in symptoms occurs later and is less

Table 4 Effects of implantation on individual symptoms of Parkinson's disease

Symptoms of Parkinson's disease Off	First significant change (months)	Peak change	Peak month	Mean (range) at end of follow-up of 36 months
Facies	1	70 %	30	70 % (100–33.3)
Rigidity	1	57.91 %	18	50 % (66.67–33.3)
Postural stability	5	57 %	18	43.75 % (100–0)
Rising sitting position	2	66.67 %	24	64.5 % (100–0)
Speech	2	64.58 %	24	41.67 % (75–0)
Bradykinesia	5	50 %	36	50 % (83.3–0)
Gait	5	50 %	30–36	50 % (83.3–0)
Tremor	24	35.65 %	24	35.6 % (50–12.5)

pronounced during the first year than when adrenal medulla grafts or coimplants are used. Although after fetal transplantation, [23, 25] clinical progress is detected 3–4 months after surgery in some of the patients, overall, it is not until the 5th month that recovery is statistically significant, becoming qualitatively and quantitatively more marked in the 7th month. Although the clinical improvement is moderate over the first 7 months, later on, in contrast to our perfused adrenal medulla transplant recipients [22], these Parkinson's patients continue to recover, with improvement peaks at postoperative months 12–18 and progressive gains until months 30–42. The recipients of AM + PN implants represent a mixed situation [24] since they improve earlier than those receiving fetal tissue [23, 25], as do the recipients of perfused adrenal medulla [20–22]. However, they differ from the latter in that they exhibit a second wave of recovery after the first postimplantation year, similar to that observed in fetal implant recipients.

The causes of improvement still remain a matter of hypothesis. Two separate but complementary sets of causes or mechanisms have been proposed for this recovery: on the one hand, those related to the viability and integration of the implanted cells and, on the other, those secondary to the enhancement of the striatal cells of the host and/or to the activation-repair-modification process of the basal ganglia circuits of the recipient. The comparison of the clinical course of the patients in this pilot study with that of our earlier series of perfused adrenal medulla and fetal ventral mesencephalon recipients [20–25] allows us to theorize as to the causes or factors governing this improvement in our model.

How can we explain the early gains observed in recipients of adrenal medulla implants (whether consisting of perfused adrenal medulla or coimplants) given the later progress observed in our series of fetal tissue recipient? What differentiates the adrenal medulla implants from the AM + PN coimplants, making the course of improvement in the cografts an intermediate situation between adrenal medulla implants and fetal grafts? The improvement observed in the early postimplantation months may be a consequence of a number of causes or factors. The reduction in medication and the motor and psychiatric complications observed in our patients in the early weeks may be due, firstly to the release of dopamine and/or other factors by the cells injured during tissue preparation and, secondly, to surgical trauma. The edema surrounding the needle track and/or the minor hemorrhage in the operative field may act as traumatic factors. The inflammatory-immunological response of the host tissue and the presence, initially, of debris and injured cells and, subsequently, of the implanted adrenal medulla and peripheral nerve tissues may trigger a cascade of events in the host caudate cells, in which secondarily activated glial cells may play the major role.

If the clinical differences among the three implant series lie in the type of tissue implanted, it appears obvious that the grafted cells (and cell injury) may play different roles in the recovery produced by each type of implant. Theoretically, the adrenal medulla tissue would exert its effect, either through direct (secretory?) action of the cells on the host fibers or through indirect action involving the striatal cells [3, 14, 29] or the fenestrated vessels that it contains. However, there are few data on the survival of the adrenal medulla cells. The few autopsies performed [7, 10, 12, 14, 28, 33] have not helped to clarify this issue since only a few surviving tyrosine hydroxylase positive (TH+) cells have been detected in one case [15]. The subject, a parkinsonian patient, had received an adrenal medulla implant 30 months prior to death and had presented clinical improvement during the first 18 months. The pathological study disclosed that the graft site was necrotic and filled with macrophages; among these cells only a few surviving TH(+) cells could be observed. Surrounding the implant, especially on its ventral aspect, there was a dense network of TH-immunoreactive terminals and processes. The authors suggest, and we agree, that this response might represent sprouting by residual host dopaminergic cells secondary to injury. We should also mention that the possibility that the sprouting may have been mediated by the implanted cells can not be ruled out since, when the pathological study was performed, the patient had re-

turned to his preoperative clinical situation and, by then, the chromaffin cells may have been dead. To our knowledge, there are no data from autopsies carried out in patients who, at death, were in better clinical condition than prior to implantation.

Although we have stated [21–23, 25] that the cause of the improvement during the first postimplantation months may be related to indirect or direct effects of the implanted cells or of the traumatic injury to the host and that this progress becomes stable during the first year, how can it be explained that recipients of AM + PN implants continue to improve during the second postoperative year? The only possible conclusion is that the incubation of PN with AM and its subsequent implantation has an impact either on the survival of the adrenal medulla cells (and supposedly on their phenotype as well), [4, 14, 31] maintaining the tropic-trophic influence on the host cells or, perhaps, the peripheral nerve (consisting of fibroblasts, schwann cells, etc.) provokes a direct mediator effect on the growth of the host fibers [6, 32] or an indirect effect through the recipient striate cells. To date, there are no pathological data from parkinsonian patients to support any of these hypotheses. Only animal studies are available [4–6, 14, 31, 34], showing that implantation of peripheral nerve in combination with adrenal medulla increases the survival of chromaffin cells and enhances the recovery of the surviving host nigrostriatal dopaminergic cells.

Thus, we conclude that, in our implant model, there appears to be more than one cause for the improvement. The surgical lesion, caudotomy and a frontal transcortical approach to the lateral ventricle, could partly explain the recovery observed in the third series. However, the differences among the respective courses following implantation of perfused adrenal medulla, fetal tissue, and coimplants suggests that, while in adrenal medulla implants, the major factor may be related to injury to the host cells and that, in fetal tissue implants, the primary factor influencing the improvement in the 2nd and 3rd years may be the implanted dopaminergic cells, in the case of AM + PN implants, we have to suppose that the fact that the recovery continues to progress during the second postoperative year is mainly due to the peripheral nerve or to its maintenance of the adrenal medulla cells. The results of this pilot study are sufficiently encouraging to induce us to carry out a broader clinical trial.

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