[18]F- fluorodopa PET scans demonstrated between 90% and 306% increased uptake in the striatum at 2.7 and 3 years after CST. Patient 1 died 44 months after transplant and patient 2 died at 52 months after transplant, from unrelated causes.

At autopsy, the number of striatal dopaminergic cells (reflected by tyrosine hydroxylase positive (TH+) immunoreactivity) corresponded to 15-30% of transplanted dopaminergic cells, and innervated the surrounding striatum. In patient 2, surviving cells were absent on the left side. Only 4-8% of cells survived in the midbrain grafts. Subtyping of grafted TH+ striatal cells revealed that 68-71% expressed the K+ channel protein, Girk2, found in the ventral tier of dopaminergic neurons of the SN pars compacta in normal tissue. Only 26-48% of grafted TH+ cells expressed calbindin, present in dopaminergic neurons of the ventral tegmental area and lateral SN. There was no inflammatory response around surviving cells, but activated microglia and macrophages only along needle tracks.

COMMENTARY

Mendez and colleagues present the first autopsy report of patients receiving fetal ventral midbrain CST for PD. In this study, the 2 patients had significant clinical improvement, as well as a functional imaging response corresponding to surviving grafted dopaminergic neurons. The unfortunate failure of CST in the left putamen of patient 2 served as negative control, as this patient's PD symptoms progressed on the right. Previous studies used solid tissue from fetal midbrain, and there are a number of significant differences in outcomes.[1, 2] Solid tissue transplant recipients have suffered from highly debilitating off dyskinesias. In contrast, both patients reported here experienced reduction in frequency and severity of levodopa-induced dyskinesias, and off dyskinesias were absent.

The difference in outcomes raises many questions, largely because of lack of standardization of cell transplant protocols from center to center. First, the role of immunosuppression has been much debated: in this study. Despite cyclosporine administration for only 6 months, graft survival was significant at autopsy, and there was no significant inflammatory response at the graft sites. This contrasts with inflammatory reactions observed around the cases of solid fetal midbrain transplant recipients who have come to autopsy. Second, the way in which tissues are treated prior to transplantation varies: Mendez et al exposed cells to GDNF, which has diverse positive effects on dopaminergic cell survival and function. Third, and importantly, Mendez et al address the thorny issue of patterns of re-innervation. If cell transplants are to function optimally, then dopamine needs to be appropriately delivered. Girk2+ TH+ neurons of the ventral SN pars compacta innervate mostly the posterior part of the putamen, and are the prevalent degenerating neurons in PD.

Dopaminergic re-innervation of this striatal compartment is thought to be necessary for alleviation of motor symptoms in PD. Many transplanted fetal neurons indeed differentiated to Girk2+ TH+ neurons, resembling native dopaminergic SN pars compacta neurons. Moreover, they re-innervated the posterior putamen. Despite small numbers of patients, these results are encouraging and, based on findings in this paper, focusing on isolation and expansion of dopaminergic neurons that differentiate to Girk2+ TH+ neurons for CST may be a promising strategy for restorative therapy in PD.

References

1. Freed CR, et al. Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. *N Engl J Med*. 2001;344:710-719.
2. Olanow CW, et al. A Double-Blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease. *Ann Neurol*. 2003;54:403-414.

Clipping vs Coiling for Ruptured Intracranial Aneurysms

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Vice Chairman, Professor of Clinical Neurology, Weill Medical College, and Chief, Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital

Dr. Fink reports no consultant, stockholder, speaker's bureau, research, or other relationship related to this field of study.

Synopsis: *In a randomized trial of neurosurgical clipping versus endovascular coiling for ruptured intracranial aneurysms, endovascular coiling was more likely to result in independent survival at 1 year.*

Source: Molyneux AJ, et al. International Subarachnoid Aneurysm Trial (ISAT) of Neurosurgical Clipping Versus Endovascular Coiling in 2143 Patients with Ruptured Intracranial Aneurysms: A Randomized Comparison of Effects on Survival, Dependency, Seizures, Rebleeding, Subgroups, and Aneurysm Occlusion. *Lancet*. 2005;366:809-817.

THE ISAT TRIAL CLOSED RECRUITMENT AND PUBLISHED preliminary results (*Lancet*. 2002;360:1267-1274.) after an interim analysis showed the benefit of endovascular treatment on the primary outcomes: death or

dependency at 1 year. This report gives the final results after complete follow-up of all randomized patients.

The 2143 patients with ruptured intracranial aneurysms, who were appropriate candidates for either clipping or coiling, were randomized to either group, treated at a neurosurgical center in the United Kingdom or Europe, and followed for at least one year after treatment. The primary outcome measure was death or dependency (modified Rankin Scale of 3 to 6) at one year, but the rates of rebleeding and seizures after treatment were also measured and compared. Baseline characteristics at enrollment were similar between treatment groups and, overall, 88% of patients were in good clinical grade (WFNS 1 or 2), 95% of the aneurysms were in the anterior circulation, and 90% were smaller than 10 mm. Patients were not randomized if the treating physicians felt that aneurysm anatomy mandated a specific form of treatment.

After one year of follow-up, 250 (23.5%) of 1063 patients randomized to endovascular treatment were dead or dependent, compared with 326 (30.9%) of 1055 patients randomized to neurosurgical clipping, an absolute risk reduction of 7.4% (95%, CI 3.6-11.2, P = 0.0001). With a mean follow-up of 4 years for all patients, the survival advantage for endovascular treatment was maintained. In the endovascular group, the risk of seizures was significantly lower, but the long-term rate of re-bleeding was higher.

COMMENTARY

The technology and expertise surrounding endovascular treatment for intracranial aneurysms has improved dramatically, and the ISAT study clearly demonstrates that the one year outcome is better for those patients that have a good clinical grade with small aneurysms in the anterior circulation. Many patients were excluded from randomization because treating physicians felt that one type of treatment was preferred. Elderly patients, very young patients, those with a poor clinical grade, and those with large aneurysms (greater than 10 mm.) or posterior circulation aneurysms were mostly treated outside of the study. Therefore, the ISAT provides guidance for a subset of patients with aneurysmal subarachnoid hemorrhage. In addition, although the mean follow-up is 4 years, we still do not have meaningful data about the long-term (greater than 10 years) results of endovascular treatment. Only 92.6% of endovascular procedures were completed, and only 66% showed complete aneurysm occlusion on follow-up angiography. What will happen to those patients who have partial occlusion of their aneurysm?

The reduction in risk of seizures in the endovascular group is an important observation, and we look forward to more information about this finding in future publications, as well as a comparative study of the long-term cognitive impairments in these patients.

Finally, we must never forget that even in this middle-aged, good clinical grade, small aneurysm population, the overall rate of death and disability at one year still exceeds 25%. There is still much to be done in addition to clipping and coiling of aneurysms if we are to make a significant impact on the natural history of this devastating disease. ■

Sleepwalking: More Often Neurological Than Psychiatric

ABSTRACT & COMMENTARY

By Charles P. Pollack, MD

Professor, Clinical Neurology, Weill College of Medicine

Dr. Pollack is a stockholder and on the speaker's bureau for Cephalon.

Synopsis: *Successful treatment of SDB, which is frequently associated with chronic sleepwalking, controlled the syndrome in young adults.*

Source: Guilleminault C, et al. Adult Chronic Sleepwalking and Its Treatment Based on Polysomnography. *Brain.* 2005;128:1062-1069.

Sleepwalking (somnambulism) is an abnormal liberation of motor activity during slow-wave sleep Because of the association with stage 3-4 sleep, episodes usually occur during the first few hours of sleep. There is little or no awareness or recall by the sleeper. Diagnosis may be made after excluding REM-Sleep Behavior Disorder, night eating and epilepsy. A sleep recording (polysomnogram) will often reveal brief arousals during sleep-wave sleep, which are not necessarily associated with gross motor activity. Most often, the patient is a child, but sleepwalking may persist into or even appear during adulthood. Surveys have shown that it affects 2% to 5% of the adult population. Serious injuries have occurred while sleepwalking, as well as acts of violence. It can usually be suppressed or rendered innocuous with small doses of benzodiazepines (lorazepam, diazepam).

In this study, fifty young adult sleepwalkers and 50 non-sleepwalkers underwent detailed diagnostic evaluation, including interview of bed partners, sleep-deprived and non-deprived EEGs (sleepwalkers only) and