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COVER STORY



Fetal Neural Transplants in Parkinson's by Kapil Gupta, M.D.

A man is taking short shuffling steps on a city sidewalk. He begins to accelerate as if he were chasing his own shadow and he falls to the ground. A concerned citizen helps him to his feet and there he stands, stooped, his left hand shaking rhythmically as if he were swirling something in his palm, his face bearing an emotionless expression.

This man, along with a million or so Americans like him, are Parkinson's patients. They live with slow movements, rigidity of the limbs and resting tremors which may, in addition to the hands, affect the legs or lips or tongue or neck. The tremors and the rigidity and the difficulty in movement in some cases become so incapacitating that the person is unable to effectively care for himself.

So when news reports showed a Parkinson's patient who had just undergone a novel neurosurgical procedure get up from bed and run down the hospital's east wing, there was a renewed optimism in the minds of many. And now this medical advancement has taken on a newer and larger life as a new study

reports that this procedure is capable of producing a long-term benefit in Parkinson's patients.

The clinical picture

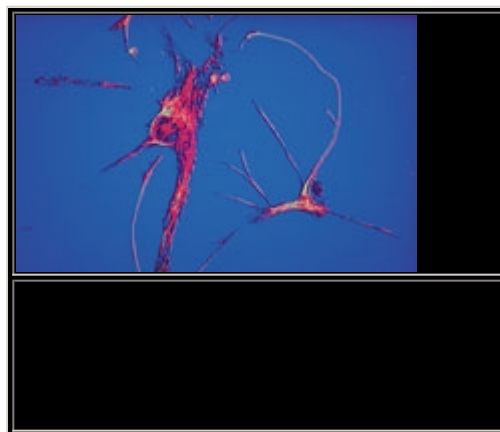
Parkinson's disease is a disorder of movement that results from a deficiency of the brain neurotransmitter dopamine. Neurotransmitters are chemicals that allow for communication between neurons. The structures in the brain that are intimately involved with movement are collectively referred to as the basal ganglia, and they utilize dopamine as one of their primary neurotransmitters. A loss of dopamine-secreting cells in one of the basal ganglia structures, the substantia nigra, is what is responsible for the dopamine reduction and, ultimately, for the Parkinson's symptoms. However, the cause of this neuropathology remains unclear.

In fully mature disease the clinical picture is strikingly obvious: stiffness and slowness of movement, stooped posture, fixed facial expression and limb tremor that subsides with movement. Difficulties in voluntary movement are a hallmark of the disease and they are termed dyskinesias. The muscle rigidity and tremor ultimately progress to a such a degree as to leave the patient incapacitated.

Treating the disease

Since Parkinson's results from a decrease in brain dopamine, treatment efforts are aimed at restoring the level of brain dopamine. Administering dopamine itself, however, is ineffective since it does not cross the blood-brain barrier and, therefore, is unable to gain entry into the brain. As a result, the most effective treatment modality involves the administering of levodopa, which is a metabolic precursor of dopamine and crosses the blood-brain barrier. Although levodopa is converted to dopamine in the brain it also undergoes a similar fate in the blood and peripheral tissues in route to the brain. In fact, 95% of orally administered levodopa undergoes chemical transformation to dopamine prior to reaching the brain.

Therefore, another drug is given concurrently with levodopa, which inhibits the enzyme that converts levodopa to dopamine, allowing for a greater percentage of levodopa to reach the brain and at a much lower dose. This drug is called carbidopa, and since it is unable to cross blood-brain barrier it does not affect the transformation of levodopa to dopamine where it is needed most: in the brain.



Levodopa treatment has demonstrated a reduction in symptom severity by more than 50%, and it has proved to be effective in improving patients' mobility, rigidity and tremor.

However, pharmacologic benefit rarely comes without a price, and levodopa is no exception. Early side effects of levodopa therapy include nausea and vomiting. Though this may seem harmless, more serious symptoms occur with time. Long-term levodopa therapy often results in involuntary movements such as head bobbing, grimacing, restlessness and abnormal movements involving the trunk and limbs. Also, many patients undergoing levodopa treatment experience fluctuations in their response to the drug. This has been termed the "on and off" phenomenon, the "on" representing the period of time during which the patient is responding to the medication and the "off" representing the period of time the patient is not responding. Ultimately, the disease often progresses to such a degree as to be refractory to levodopa treatment.

Given the suboptimal long-term efficacy of treatment with levodopa and other medicines, alternative forms of treatment must be seriously entertained.

Fetal tissue transplants

The rationale for the fetal tissue transplants approach is that the transplantation of fetal dopamine-producing neurons into the region of the basal ganglia will allow these neurons to establish effective connections with other neurons and, by virtue of their dopaminergic production, help to increase the level of dopamine in this system of the brain to normal levels. If such a procedure is effective it would not only result in an improvement in patient symptoms but it would decrease the amount of levodopa the patient would require.

The brain tissue is obtained from immature fetuses of mothers who have undergone an elective abortion. Then, following procedural guidelines, tissues from the appropriate region of the fetal brain are transplanted into the Parkinson patient.

Although some studies have reported minimal benefit from the procedure, others have demonstrated an impressive improvement in patient symptoms. This has been shown to be a result of various factors, one of them being the amount of dopaminergic neuron tissue that is implanted.

One study that demonstrated an encouraging result involved four Parkinson patients. The researchers implanted fetal tissue into the brains of these four Parkinson patients and found clinical improvement in all four. They found that the patients experienced a longer duration of "on" time without a substantial change in the dosage of medication. Also, they found that the patients' dyskinesia (impaired ability to make voluntary movements) had practically disappeared.

Another study involved a 59-year-old man with an eight-year history of Parkinson's disease. The patient's symptomatic improvement on carbidopa-levodopa had begun to subside and he then began to experience dyskinesias during the "on" period, along with a worsening of gait and a mild postural instability. The symptoms became so troublesome that he was forced to stop working.

Researchers grafted fetal neurons into his brain and later assessed the results. Within one and three months following transplantation, the patient's dyskinesias and motor symptoms had disappeared, the "off" time had improved considerably, and the amount of "on" time with dyskinesia had also improved. In addition, the dose of carbidopa-levodopa treatment required to sustain him had been reduced substantially as a direct result of the transplant.

Long-term benefits

If any new treatment is to be useful it must demonstrate a sustained benefit to the patients involved. One issue that has been of primary concern is the long-term outcome of the patients who undergo this transplant procedure. Since an improvement in these patients' symptoms is a direct result of the transplanted fetal dopamine neurons, it is only logical that a demonstration of long term viability of this transplanted tissue would also result in long-term therapeutic benefit.

A recent study has demonstrated just that. The study involved a 69-year-old Parkinson's patient who was responsive to levodopa therapy for six years before she began to experience "on/off" phenomena. She underwent fetal transplantation three years later.

Following the procedure her rigidity and hypokinesia (slowness of movement) gradually improved, as did the "on/off" phenomena, and levodopa could be withdrawn after 32 months (though it was later reinstated at a low dose). The patient continued to function well with only low dose levodopa treatment and has continued to do so for ten years following the transplant procedure.

It is important in such circumstances to establish a causal relationship between the performance of the implanted tissue and the patient response. So in order to measure the amount of dopamine released from the transplanted tissue, the researchers used a dopamine antagonist called [¹¹C]-raclopride (RAC), which binds to the D₂ dopamine receptor. The binding of RAC to the dopamine receptor was then demonstrated by a noninvasive imaging tool called the positron emission tomography (PET) scan.

Their results indicated that the neurons from the fetal graft were releasing dopamine in sufficient amounts. More importantly, it demonstrated that these transplanted neurons have proved to be resistant to the Parkinson's disease process for ten years. Therefore, the study demonstrated not only an impressive clinical improvement in the patient's symptoms, but also in graft viability and function in vivo, rather than at postmortem examination.

Future directions

This study settles a large concern of this therapeutic procedure, namely the long-term viability of grafted fetal dopamine neurons and their capacity to help restore dopamine levels in the brain. While the study is an important one, however, it cannot be overlooked that it involved only a single patient. Therefore, it is important to develop further studies on fetal transplants for Parkinson's disease, and this experiment, by virtue of its promising results, should trigger a greater investigative enthusiasm in this area of medicine.

Another consideration is not only the ethical nature but also the availability of aborted fetal tissue. The supply is certainly limited and, this being the case, some researchers have entertained the possibility of using nonhuman donor cells for neural transplants in Parkinson's disease.

One group effectively demonstrated the survival of a neural graft using pig neurons at postmortem examination, seven months following the procedure. This study was the first to document survival of a neuronal xenograft in the human brain. It also demonstrated an effective growth of nonhuman dopamine neurons as a potential therapeutic tool for Parkinson's disease patients, another first.

Despite recent advances in such procedures, neural transplantation for Parkinson's disease remains an experimental phenomenon, and controlled, more detailed, investigations are necessary for it to become an accepted mainstream therapy for the disease.

So if you should, in the future, see our man on the sidewalk, perhaps you will see in a different light. Perhaps his hands will be still and his gait steady. And perhaps you will then feel free to focus on his eyes, and allow him to watch you do so.

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Find Out More...

For further information on fetal neural transplants, contact:

University of Florida
Tampa, Florida
Department of Neurological Sciences
Dr. Robert Hauser
813.253.4077

Studies with pig fetal cell transplants on humans are forthcoming. As a general rule, patients who have Parkinson's disease and have been taking Sinemet for five to ten years are eligible to participate in the studies. Motor fluctuations and mental capacity should be in good status. Patients should be available for review every three to four months.

University of Colorado School of Medicine
Denver, Colorado
Department of Medicine
Sharon Culver
Fetal Neuron Transplant Coordinator
303.315.6927

McLean Hospital
Belmont, Massachusetts
Department of Neurology
Dr. Ole Isacson
Director of Neuro-Regeneration Lab
617.855.2000

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