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Treatment of Parkinson's Disease through Fetal cell transplantation, Gene therapy & Surgery.

Submitted by: Haitham Hussain Elmatri
Student No: 1102
Supervisor: Dr Nowar
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Abstract:
Parkinson's disease symptoms can be reduced with intra-striatal transplantation of human fetal mesencephalic tissue, rich in dopaminergic neurons, in Parkinson's disease (PD) patients show that cell replacement can work and, in some cases, induce major, long-lasting improvement.[1] Gene therapy can also be used and it involves the insertion of genes that provide specific genetic instructions that cells use to produce a desired protein. The treatments produce proteins that are involved in normal cellular processes and may therefore be less likely to cause side effects. Moreover, gene therapy can be targeted to a specific location where the treatment is needed, which also may limit possible side effects.[2] Finally, Patients who fluctuate between "on medication" and "off medication" states are usually good candidates for the surgical intervention which are Thalamotomy and pallidotomy & Deep Brain Stimulation. The major risk associated with surgical procedures is a 2% risk of stroke.[3]

Introduction:

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. Early in the disease, the most obvious are shaking, rigidity, slowness of movement, and difficulty with walking. Thinking and behavioral problems may also occur. Dementia becomes common in the advanced stages of the disease. Depression and anxiety are also common, occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems. The main motor symptoms are collectively called "parkinsonism", or a "parkinsonian syndrome". The cause of Parkinson's disease is generally unknown but believed to involve both genetic and environmental factors. The motor symptoms of the disease result from the death of cells in the substantia nigra, a region of the midbrain. This results in a decrease in dopamine in these areas. The reason for this cell death is poorly understood but involves the build-up of proteins into Lewy bodies in the neurons. Diagnosis of typical cases is mainly based on symptoms, with tests such as neuroimaging being used to rule out other diseases.

Discussion

1. Cell Transplantation for Parkinson Disease Two Case Reports

Recent advances in stem cell technologies have rekindled an interest in the use of cell replacement strategies for patients with Parkinson disease. This study reports the very long-term clinical outcomes of fetal cell transplantation in 2 patients with Parkinson disease. Such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation. Two patients received intra-striatal grafts of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts, as restorative treatment for their Parkinson disease. To evaluate the very long-term efficacy of the grafts, clinical assessments were performed 18 and 15 years post-transplantation. Motor improvements gained gradually over the first postoperative years were sustained up to 18 years post-transplantation, while both patients have discontinued, and remained free of any, pharmacological dopaminergic therapy. The results from these 2 cases indicate that dopaminergic cell transplantation can offer very long-term symptomatic relief in patients with Parkinson disease and provide proof-of-concept support for future clinical trials using fetal or stem cell therapies. [1]

2. Gene Therapy

Gene therapy has a number of potential advantages that may be useful in progressive medical conditions. Conceptually, it is a means of making cells produce a protein that they normally do not produce that might improve a particular condition. The technique inserts genes that provide specific genetic instructions that cells use to produce a desired protein. The treatments produce proteins that are involved in normal cellular processes and may therefore be less likely to cause side effects. Moreover, gene therapy can be targeted to a specific location where the treatment is needed, which also may limit possible side effects. Finally, gene therapy does not rely on the placement of devices that may fail due to mechanical or electrical reasons. A number of proteins have already been used for gene therapy for Parkinson's disease. The choice depends on the treatment strategy. For example, one strategy is to improve the delivery of dopamine to the relevant brain regions in Parkinson's disease. Other strategies have tried to provide growth factor support to brain regions with the expectation that this might help damaged nerve cells to recover and thus slow Parkinson's disease progression or reverse it. Gene therapy relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells. Because human bodies have developed a number of enzymes that breakdown unprotected DNA, most gene therapies use some sort of "protective envelop", called a vector, to carry the genetic material and deliver the gene to targeted cells. The most common vectors include adeno-associated virus type 2, lentivirus, adenovirus, and herpes simplex virus. Only viruses that have lost their ability to reproduce themselves and cause disease are selected as vectors for gene therapy. Adeno-associated virus type 2(AAV-2) has particular advantages. It carries genetic material only to neurons (not to the other supporting cells of the brain) and once within the brain it is particularly efficient in carrying the genetic material to the neurons affected in Parkinson's disease. Most gene therapy studies in Parkinson's disease have used AAV-2 as the vector. Lentiviruses have also been studied extensively. Because of their larger capacity, lentivirus is the vector when more than

one gene is used. Once a gene and vector have been selected, the treatment must be administered to the relevant area of the brain. The studies performed thus far have been directed to particular regions of the basal ganglia. To date, gene therapy for Parkinson's disease has been administered by drilling a hole in each side of the skull and then injecting the selected dose of the viral vector (containing the gene) into the desired brain region (either putamen or subthalamic nucleus) using image-guided surgical techniques. These treatments are performed either in a standard operating room or in a specialized radiology suite. Recovery from these procedures is usually quite rapid, with most patients being discharged home 1 or 2 days after gene therapy. [2]

3- Surgical Treatment

The surgical treatment options for patients with Parkinson's disease are expanding. Deep brain stimulation **(**DBS) surgery offers important symptomatic relief in patients with moderate disability from Parkinson's disease who still retain some benefit from antiparkinsonian medications and who are cognitively intact. Patients who fluctuate between "on medication" and "off medication" states are usually good surgical candidates. The major risk is a 2% risk of stroke, due to bleeding in the brain. DBS requires regular neurological follow-up and periodic battery changes. It reduces, but does not eliminate, symptoms of Parkinson's disease. The time to consider DBS surgery is when quality of life is no longer acceptable on optimal medical therapy as administered by an experienced neurologist. When medication adjustments do not alleviate motor fluctuations or when side effects from medications cause significant problems, surgical treatment of Parkinson's disease may be considered. Two recent studies have shown advantages of deep brain stimulation over best medical therapy in appropriated selected patients with Parkinson's disease. Selection criteria for these studies included levodopa responsiveness and persistent disabling fluctuations. Patients were excluded for atypical syndromes, dementia, and continuing drug or alcohol abuse. Thalamotomy and pallidotomy were the first surgical procedures developed and are brain lesioning procedures. To perform them, the surgeon uses a small heat probe to destroy a small region of brain tissue that is abnormally active in Parkinson's disease. No instruments or wires are left in the brain after the procedure, which produces a permanent effect on the brain. In general, it is not safe to perform lesioning on both sides of the brain. Thalamic surgery is generally reserved for patients with essential tremor and is not recommended for patients with Parkinson's disease. Pallidotomy is the standard ablative procedure. Deep brain stimulation surgery involves placing a thin metal electrode into either the globus pallidus or subthalamic nucleus. A programmable pulse generator is implanted subcutaneously beneath the clavicle. A subcutaneous extension wire connects the pulse generator to the brain electrode. The stimulator can be adjusted during a routine office visit by a physician or nurse. Unlike lesioning, DBS does not destroy brain tissue**.** Instead, it reversibly alters the function of the brain tissue in the region of the stimulating electrode. Although DBS is a major advance, it is a more complicated therapy that may demand considerable time and patience before its effects are optimized.[3]

Conclusion:

In conclusion, Parkinson's disease remains uncurable and there is still much work to do in order to understand how to completely cure the disease. However, these treatment options represent an important means of alleviating the discomforting symptoms that the patients suffer from and subsequently leads to a decrease in the quality of their life.

References:

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