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REVIEW

Clinical neurorestorative progress in Parkinson's disease

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Abstract: Parkinson's disease (PD) is one of the common neurodegenerative diseases. Besides the symptomatic therapies, the increasing numbers of neurorestorative therapies have shown the potential therapeutic value of reversing the neurodegenerative process and improving the patient's quality of life. Currrently available novel clinical neurorestorative strategies include pharmacological managements (glial cell-line derived neurotrophic factor, selegiline, recombinant human erythropoietin), neuromodulation intervention (deep brain stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation), tissue and cell transplantation (fetal ventral mesencephalic tissue, sympathetic neurons, carotid body cells, bone marrow stromal cells, retinal pigment epithelium cells), gene therapy, and neurorehabilitative therapy. Herein, we briefly review the progress in this field and describe the neurorestorative mechanisms of the above-mentioned therapies for PD.

Keywords: Parkinson's disease, clinical study, neurorestorative treatment, cell transplantation, neuromodulation

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, with main symptoms of stiffness, slowing of movement, and postural instability.[1] Dementia commonly occurs in the advanced stages of the disease, whereas depression is the most common psychiatric symptom. PD affects approximately seven million people globally and one million people in the USA.[2] The prevalence of PD is about 0.3% in the whole population of industrialized countries. PD is more common in the elderly and prevalence rises from 1% in those >60 years of age to 4% in the population aged >80 years.[3]

The main pathological characteristic of PD is cell death in the substantia nigra and, more specifically, the ventral (front) part of the pars compacta, affecting up to 70% of the cells by the time death occurs.[4] The occurrence of Lewy bodies is a key pathological feature of PD.[5]

The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a L-3,4-dihydroxyphenylalanine (DOPA) decarboxylase inhibitor or catechol-*O*-methyl transferase inhibitor), dopamine agonists, and monoamine oxidase-B inhibitors.[6] Most patients with PD eventually need levodopa and later develop motor side effects. When medications are not enough to control symptoms, surgery and deep brain stimulation (DBS) can be of use.[7] Several attempts have been made to stimulate the neurorestorative process for nigral and/or striatal dopaminergic

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system by using pharmacological factors, gene expression, exercise, neuromodulation, and cell therapies.

Clinical neurorestorative progress

Medicines

Glial cell-line derived neurotrophic factor (GDNF), infused unilaterally into the putamen for 6 months, could exert significantly sustained bilateral benefits and improve the quality of life in patients with PD.[8] Supplementation with antioxidants such as selegiline, which have been used as monotherapy in early PD or in combination with levodopa in more advanced disease, might prevent or reduce the rate of progression of PD.[9] Recombinant human erythropoietin (rhEPO) had beneficial effects on nonmotor symptoms but not on motor function. Nonmotor symptoms, such as cardiovascular autonomic dysfunction and cognition, which were refractory to dopaminergic treatment, showed improvement after the administration of rhEPO.[10]

Neuromodulation

Deep brain stimulation

Deep brain stimulation is recommended for people who have PD with motor fluctuations and tremor inadequately controlled by medication and for those who are intolerant to medication.[7] DBS was first used by implanting multiple electrodes into the subcortical structure for treating hyperkinesis,[11] then into the thalamus to treat tremor due to advanced PD in 1987, and, from 1993 onward, into the subthalamic nucleus or the globus pallidus.[12] Furthermore, another study showed that DBS significantly improved psychological conditions, including depression, somatization, fear, anxiety, and psychosis, factors included in the symptoms checklist (SCL)-90, of patients with PD.[13] After DBS treatment, levodopa dose was reduced by about 54.5%. In contrast, levodopa dose was increased by 20.5% in the 36th month in the control group.[14] Due to the poor survival of dopaminergic cells after transplantation, DBS might be combined with cell therapy to manage PD in the future.[15] A multitarget strategy aimed at improving symptoms with different pathogenetic mechanisms might be a promising approach in the near future.

Transcranial stimulation

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are noninvasive cortical stimulation methods that can benefit patients with PD and other movement disorders. Koch et al[16] reported that rTMS at 1 Hz could markedly reduce drug-induced dyskinesias, whereas 5-Hz rTMS induced a slight but not significant increase. However, a systematic review revealed that high-frequency rTMS showed effects on motor signs in PD, during assessment with the Unified PD Rating Scale (UPDRS), and that low-frequency rTMS had only limited effect.[17] Combination of the two should be encouraged; some evidence showed that preconditioning 1-Hz rTMS over primary motor (M1) by anodal tDCS could improve hypokinetic gait in patients with PD.[18] Combined with physical training[19] or dance therapy,[20] tDCS could improve gait and balance in patients with PD. An open-label study[21] showed that high-frequency repetitive deep TMS (rDTMS) might be a safe treatment for PD motor symptoms. The researchers used H-coils, inducing deeper and wider magnetic fields, over 12 rDTMS sessions spanning a period of 4 weeks at excitatory (10 Hz) frequency over the M1 and bilateral prefrontal regions.[21]

Magnetic resonance-guided focused ultrasound surgery

The neuromodulation potential of ultrasonography was first described by Fry et al[22] in the 1950s, and the work is still in a preliminary stage. The new technique of magnetic resonance-guided focused ultrasound surgery (MRgFUS) was first used for cancer treatment.[23] The method is currently the subject of many experimental and clinical trials, and it appears to be particularly promising in the ablation of tissues located deep in the brain and signifies the beginning of interventional neurology and an alternative to neurosurgery. The procedure does not require anesthesia and avoids the creation of a burr hole.[24] The safety and effectiveness of this method have been observed in parkinsonian and essential tremors.[25] More data and long-term follow-up will be required to learn whether ablative lesioning via FUS will lead to better outcomes with lower risks.

Neurorehabilitation

Rehabilitation as a complementary neurorestorative strategy can help patients with PD to maintain their quality of life. A randomized controlled trial showed that home-based, individualized occupational therapy led to an improvement in self-perceived performance in daily activities.[26] Moderate-to-strong evidence exists for task-specific benefits of targeted physical activity training on motor performance, postural stability, and balance.[27] Rhythmic auditory stimulation as a neurorehabilitative strategy for gait training could improve gait velocity, stride length, and step cadence in patients with PD.[28] Efficacy of a physical therapy in patients

with PD was confirmed by a randomized controlled trial.[29] Most recently, a 2-year follow-up study demonstrated that intensive exercise in the early stages of the disease might slow down the progression of motor decay and it might delay the need for increasing drug treatment.[30] Today, exercise training is widely used for rehabilitation of patients with PD. The short-term benefits from physiotherapy in PD have been clearly known and there are no differences between the different types of physiotherapy interventions.[31,32]

Tissue graft and cell therapy

Backlund et al[33] first reported the transplantation of autologous adrenal medullary tissue into the striatum in two patients with severe PD, which showed some beneficial effects. Cell or tissue transplantation can potentially restore neurosurgical functions in patients with PD. Since then, numerous cell or tissue replacement therapies have been developed and tested.

Fetal ventral mesencephalic tissue

Clinical use of fetal ventral mesencephalic tissue as a treatment to replace dopaminergic neurons in patients with PD was first done 30 years ago. Dopamine neurons were transplanted ectopically into the striatum. They could structurally compensate for lost cells, form synaptic contacts with host neurons, release dopamine, restore dopamine transmission, and positively moderate gradual improvements in motor function in patients with PD.[34–37] More important evidence that is accumulating shows that *L*-3,4-dihydroxy-6-[18F]fluoro-phenylalanine (^{18}F-DOPA) uptake increased significantly in the grafted striatum during a decade of follow-up by positron emission tomography (PET) studies.[34]

Two major randomized, double-blind, sham surgery placebo-controlled trials with neural grafts in PD have been performed.[38,39] Even these trials could not meet the primary endpoints, with 15%–50% graft-induced dyskinesias at the initial study stage; the outcome of each trial was different from each other. Freed et al's[38] results were better than Olanow et al's.[39] Younger patients (≤60 years of age) revealed significant improvement in the transplantation group as compared with the sham-surgery group by assessment with UPDRS and Schwab-and-England score;[38] furthermore, after following up for 2–4 years after surgery, the grafts were effective at reducing the PD motor symptoms. At 2 years, clinical improvement was almost twice the level observed at 1 year and this was sustained at 4 years. Likewise, the increase of ^{18}F-FDOPA uptake was evident at 2 years and 4 years, with significant clinical–PET correlations.[40] This strongly suggests that this therapeutic strategy may need years to reach its full effect.

Another report showed similar results; two patients were followed up for 15 years and 18 years, respectively, after surgery. One patient gradually improved his motor performance over the first 4 years posttransplantation. The other patient showed this effect until 2 years later. Importantly, they could stop their dopaminergic medication around 5 years postgraft, and motor benefits were still constant at their last assessment.[41]

Other cell therapies

Four patients with PD underwent transplantation with autologous sympathetic neurons in the unilateral intrastriatal zone and improved their performance status by reducing the time spent in the off phase.[42] Thirteen patients with advanced PD underwent bilateral stereotactic implantation with carotid body cells into the striatum, and most of them showed functional improvement 6–12 months after transplantation.[43] Bone marrow stromal cells (BMSCs) transplanted into sublateral ventricular zone by stereotactic surgery were safe, with no serious adverse events in seven patients with PD during 10–36 months of follow-up;[44] in another study, eight PD and four PD-plus patients showed improvement after BMSC transplantation during a 12-month follow-up.[45]

Human retinal pigment epithelial (hRPE) cells were transplanted into the putamen and lateral ventricles in 17 patients with PD. Three months later, the majority of patients showed functional improvement (82.4% effect in the contralateral site and 64.7% in the ipsilateral site).[46] In another study, hRPEs were implanted into the postcommissural putamen in 12 patients with PD; eleven patients showed improvement in the primary outcome measure 3 months after transplantation and showed a peak at 12 months, which then declined during the next 24 months. PET analysis showed a trend with increased dopamine release during the first 6 months.[47] Even spheramine as hRPE cell microcarrier showed some effects in patients with PD in a 1-year, open-label, single-center study;[48] recently the result of its further application was negative in a double-blind, randomized, controlled trial.[49]

Hallett et al[50] examined the expression of dopamine transporters in human fetal midbrain cellular transplants. They found that dopamine transporters were robustly expressed in transplanted dopamine neuron terminals in the reinnervated host putamen and caudate for at least 14 years postimplantation. The transplanted dopamine neurons showed a healthy and nonatrophied morphology at all time

points. The vast majority of transplanted neurons remained consistently healthy, with clinical findings of maintenance of function for up to 15–18 years in patients.[50]

Gene therapy

Nine gene therapy clinical trials for PD have been initiated and completed.[51] The first gene therapy trial, using glutamic acid decarboxylase gene with the adeno-associated virus vector, was conducted by unilateral subthalamic injection in 12 patients with PD in 2007. The procedure was safe and well tolerated by advanced patients with PD who had significant improvements in motor UPDRS scores 3 months after gene therapy and persisted up to 12 months.[52] In 2008, low dose of the AAV–human aromatic L-amino acid decarboxylase (hAADC) vector was tested in five patients with moderate-to-advanced PD, who had a modest improvement with PET evidence of sustained gene expression.[53] AAV serotype 2-neurturin (CERE-120) was delivered into the substantia nigraplus putamen in 12 patients with PD who had some functional improvements,[54] and this method with long-term follow-up was still feasible and safe.[55]

Discussion

Neurorestorative mechanisms of cell therapy for PD

Fetal midbrain tissue

Fetal brain tissue containing dopamine neurons was transplanted into the striatum of a rat model of PD in 1979, showing good survival and axonal outgrowth and significantly improving motor abnormalities.[56] Different intrastriatal transplantation techniques might affect the result; intrastriatal transplantation of partial (tissue pieces) suspension by a metal cannula could have a higher survival rate of dopamine neurons, a greater reduction in amphetamine-induced rotations (overcompensation), and more extensive fiber outgrowth.[57]

Adrenal chromaffin, carotid body cells, and retinal pigment epithelial cells

Transplants of chromaffin cells derived from adrenal medulla or carotid body cell aggregates were explored in the early 1980s.[58] hRPE cells attached to gelatin microcarriers (Spheramine) were unilaterally transplanted into the putamen and improved behavioral scores were observed in PD models, with PET confirmation.[59]

Mesenchymal stromal cells

BMSCs were transplanted into the striatum, and this improved abnormal rotational behavior in a rat model of PD.[60] Hypoxia can promote BMSC proliferation, dopaminergic neuronal differentiation, and then restore some functions after intrastriatal transplantation.[61] In addition, allogeneic BMSC[62] or human amniotic fluid stromal cell transplantation[63] could improve urodynamic pressure on voiding function in PD rats. Umbilical cord stromal cells could survive well after transplantation in a parkinsonian model[64] and partially restore functions,[65,66] as well as possessing the potential to transform into immature or mature neuron-like cells.[67] The intravenous route of cell therapy has been tried in models of PD;[68] umbilical cord blood CD34+ cells delivered by intravenous injection could ameliorate biochemical and histological motor deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonian mice and the strategy was even superior to levodopa in terms of its effect.[69]

Neural stem/progenitor cells, embryonic glial-restricted precursor cells, or embryonic stem cells

Neural stem/progenitor cells or undifferentiated embryonic stem cells when transplanted into the striatum could differentiate into neurons or dopaminergic neurons[70] and restore some functions.[71,72] Delayed transplantation of embryonic glial-restricted precursor cells by exposure to bone morphogenetic protein could restore tyrosine hydroxylase expression and promote behavioral recovery through rescuing, not preventing, pathological changes.[73]

Olfactory ensheathing cells

Olfactory ensheathing cells transplanted with ventral mesencephalic cells could get better functional neurorestoration in a rat model of PD[74] through increase in transplanted neural stem cell survival and functions[75,76] or modulation of intrinsic apoptotic pathways in parkinsonian rats.[77] Neural grafts combined with olfactory ensheathing cells can maintain the functional improvement in animals or patients with PD longer.[75]

Potential mechanisms of neuromodulation for PD

DBS in the subthalamic nucleus can significantly affect striatal dopaminergic metabolism and markedly reduce dopaminergic medication[78] or consequently activate substantia nigra compacta neurons via inhibition of gamma-aminobutyric acid-ergic substantia nigra reticulate neurons.[79] A recent study showed that high-frequency stimulation in the subthalamic nucleus could induce widespread anatomofunctional rearrangements through downregulation of Adrb1 protein.[80]

Neurorestorative mechanisms of neurorehabilitation for PD

Al-Jarrah et al[81] found that endurance exercise training could promote angiogenesis in a mouse model of PD. In addition, they found this training could decrease the expression of brain damage markers in the striatum,[82] possibly by decreasing the level of neuronal nitric oxide.[83] Strong evidence showed that long-term aerobic exercise could help functional motor and limbic circuits' reorganization in a rat model of PD[84] and that longer-duration vibration training could significantly increase the number of nigrostriatal dopaminergic neurons.[85]

Conclusion

Currently, effective approaches to relieve symptoms in patients with PD are available; however, when faced with this neurodegenerative disease, extreme pessimism and unrealistic expectations are not good for patients and their treatment. Ongoing cell-based comprehensive neurorestorative therapies have made significant progress in clinical practice. The community needs to conduct more research into each promising strategy and optimize the benefits from current progress for patients with PD.

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Disclosure

The authors report no conflicts of interest in this work.

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