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Research Article

Computer Assisted Stereotactic Transplantation of Human Neural Stem Cells in Pakinson's Disease

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Abstract

Objective: To explore the efficacy and safety of computer assisted stereotactic transplantation of human neural stem cells on Parkinson's disease (PD).

Method: With the guidance of CT and MRI image mergence, we transplanted 4 × 107 neural stem cells into the putamen and lateral ventricle of seventeen PD cases by stereotactic surgery. The transplantation site was located in the contralateral side of the symptoms and signs.

Result: After three months follow-up, the effective rate of cell transplantation was 82.4% in the contralateral site and 64.7% in the ipsilateral site. Only a minority of cases had mild dizziness and hemiparesis, but the duration was short.

Conclusion: The therapy, computer assisted stereotactic transplantation of human neural stem cells in the treatment of PD, is safe and efficient.

Keywords: Human Neural Stem Cells; Stereotaxic Technique; Cells Transplantation; Image Mergence; Pakinson's Disease

Introduction

The treatments of Parkinson's disease (PD) are mainly drug treatment, operation and cell transplantation therapy. The traditional drug treatments are effective only in the early stage of the disease, which will invalid and have side effects with the progress of the disease. The pallidotomy could get short-term curative effect. The deep brain stimulation with expensive costs is a good treatment method, but its long-term effect is not exact. All these methods are the symptomatic treatments which can't reverse the degeneration of the substantia nigra's dopaminergic neurons; therefore, they are not the real treatment methods to PD. In recent years, with the rapid development of the stem cell biology, neurobiology, neuroimaging and stereotaxic technology, the neural stem cells transplantation has become a treatment strategy to PD. It has its own advantages compare to the traditional therapy, such as supplying the lost dopamine neurons, increasing dopamine content in the corpus striatum, especially the potency of reconstructing neuromotor loop [1-3].

During January 2008 to March 2009, the people neural stem cell transplantation therapy by computer assisted stereotaxy had been taken in seventeen PD patients, and had obtained a satisfactory clinical curative effect, as follows.

Material and Methods

Research objects

Seventeen cases met primary PD diagnosis standard [4] which had positive effect by the systematic levodopa therapy and did not take the pallidotomy or deep brain stimulation therapy. The drugs' effect decreased and caused side effects with the progress of the disease. Among all cases eight for male, nine for female, from forty to seventy-six years old, averaged 61.6 years. The disease courses averaged 5.2 years from three to ten years.

Clinical classification

Sixteen cases had bilateral symptoms, among which one case was tremor type, two cases were rigid type and thirteen cases

were tremors plus rigid type. One case had unilateral symptoms with the tremor plus rigid type.

Hoehn-Yahr disease classification

One case was level I, three cases were level II, eleven cases were level III, two cases were level IV. The surgical sites were on the left sides among twelve cases and on the right sides among five cases.

Instruments

1.5 TMR; sixty-four rows helical CT; Leksell brain stereotaxic instrument; radiofrequency apparatus; Germany Brain-LAB operation plan system.

Methods

The preoperative preparation

1. All neural stem cells are provided by Interventional hospital of Shandong Red Cross Society.
2. The patients were instructed not to take any anti-Parkinson's drug one day before operation.
3. The specialized PD UPDRS scores and Hoehn-Yahr disease classification were inspected before operation.

The operation plans

1. Obtaining the image data: The brain MRI 3D SPGRS sequence without scanning angle was taken before operation. The ASA-602S stereotaxic headstock was installed by local anesthesia of the operation. Make sure the parallel between inferior framework and AC-PC projection body. Then 1.25 mm continuous straticulate scanning was taken. The CT images and MRI images were stored with the DICOM format.
2. Setting operation targets: The preoperative MRI images and CT images were imported into the Germany Brain-LAB operation plan system, and fused layer by layer by using the mutual inductance CT/MRI image fusion system The merged images were transferred to coordinate system. By the brain stereotactic map, the contralateral putamen [7,8] and lateral ventricle were selected to unilateral transplant. To the serious PD patients according to the symptom, the neural stem cells were directly transplanted into the Vim and Pvp nuclear. The symptoms were quickly relieved or disappeared by their mechanical oppression and aseptic inflammation so as to obtain "immediate" effect.

The operation processes

1. According to target spot the patients' operative cranial point was set, then drilled into the skull by local anaesthesia.
2. Insert the electrodes; Measure the impedance value of the targets.
3. Give the lowest and highest electrical stimulation to verify the accuracy of the target.
4. Change the transplant needle (inner diameter 0. 5 mm), put the neural stem cells into one millilitre empty needle, link the needle with the stem cells transplantation inner sleeve, inject 0.1 millilitre neural stem cells into each target, then stop injecting for five minutes to prevent cells to diffuse along needle passage. Withdraw the needles two times in each target, the distance of the withdrawing needle for five millimeters. The remaining neural stem cells were transplanted into ipsilateral lateral ventricle. The total number of the cells was 4×106 [9].
5. Suture wounds, cover sterile dressings, return to Intensive Care Unit. Two days postoperative the patients could recover normal activities.
6. To consolidate curative effect the patients should continue to take medicines for three to six months after operation.

Curative effect assessment

1. The curative effect evaluation standard:
   a) **Efficiency:** The symptoms of tremor and rigidity disappeared completely. Improvement: The symptoms obviously alleviated with some symptoms remain.
   b) **Inefficiency:** The symptoms did not improve.
2. The evaluation time: The evaluation time of the contralateral symptom's improvement was in the operation, 7 days post operation, 1months post operation and 3months post operation. While the evaluation time of the ipsilateral symptom's improvement was in the 1-month post operation and 3 months post operation.

Results

Effect assessment

	Intraoperation	7d Post Operation	1m Post Operation	3m Post Operation
Efficiency	11	11	14	14
Improvement	3	4	1	1
Inefficiency	3	2	2	2

Table 1: The contralateral symptomatic improvements of 17 PD patients.

	1m's Post Operation	3m's Post Operation
Efficiency	8	11
Improvement	5	4
Inefficiency	4	2

Table 2: The ipsilateral symptomatic improvements of 17 PD patients.

Postoperative adverse reactions and complications

3 patients had hemiparesis and salivating after operation. 2 patients had transient high blood pressure and dizziness because of tension.

Follow-up results

The contralateral symptoms were improved continuously after operation. The total effective rate was 88.2% and the significant efficiency was 82.4% 3 months post operation. The ipsilateral symptoms were improved after operation, and the improvements increased significantly after 1-month post operation. The total effective rate was 88.2% and the significant efficiency was 64.7% 3 months post operation. The adverse reactions such as hemiparesis and salivating recovered. The patients' self-care capacity improved obviously.

Discussion

The transplantation of the neural stem cells in the treatment of PD achieved great results in experimental and clinical aspects. Parati [10] reported that the treatment that the stem cells separated from the olfactory bulb were transplanted into the mouse's striatum showed good prospects. Zengming Tian [12] reported fifty PD patients who were given forebrain stem cells transplantation into the striatum by stereotactic technique, after eight to thirty months' follow-up, the treatment effective rate was 92% and did not have any obvious immunologic rejection.

The biology mechanism of the neural stem cell transplantation of the treatment of PD was clear and definite, it includes three types of implementation. First, transplanted neural stem cells are guided by the local microenvironment *in vivo* and differentiate into dopaminergic neurons, then the missing substantia nigra dopaminergic neurons due to trauma, disease or aged were substituted, repaired or replaced so as to improve the level of dopamine in the brain. Second, the transplanted neural stem cells provided multiple of nutritional support for the residual and damaged nerve cells by producing neurotrophic factors so as to make the substantia nigra dopaminergic neurons survive for long time and prevent substantia nigra dopaminergic neurons from degeneration. Third, the synapsis of the neuron differentiated by neural stem cells rebuilds the neural circuit and restore neural functions. Therefore, neural stem cells as dopaminergic progenitor cells were the most ideal cell resources for transplantation in the treatment of PD.

At present the most direct transplanted area was the striatum, because it was the target area where the substantia nigra dopaminergic neurons played a part. About half of the human substantia nigra dopaminergic neurons projected to putamen. In PD patients' brain, the degenerated area where the substantia nigra dopaminergic neurons dominated was mainly in the back of the putamen [8], which provided a reliable basis to the cell's transplantation.

Adult neural stem cells were mainly generated in the periventricular areas which could migrate to anywhere and replace the damaged brain cells under the action of some cell factors [15]. The transplanted neural stem cells could activate or mobilize endogenous neural stem cells in the ventricular wall migrate to the striatum and divide into dopaminergic nerve cells to play therapeutic effect [16]. Most of the neural stem cells were transplanted into back of the putamen, the rest of the neural stem cells were transplanted into ipsilateral lateral ventricle. So, some patients felt better with the contralateral symptoms besides the ipsilateral symptoms because of the reconstruction of the loop and cells internal mobilization. In addition, we also treated seven PD patients through intrathecal injection to transplant neural stem cells, and gained a reliable clinical curative effect, which supported this conclusion.

Through the follow-up we found that the transplantation of neural stem cells took remarkable curative effect after three to six months post operation. Bilateral symptoms were both improved. The improvement rate of contralateral symptoms was 82.4% and 64.7% of the ipsilateral symptoms. The clinical symptoms improved continuously, no "bounce" phenomenon. The operation effect related to the PD patients' reaction to levodopa [17], if the reaction was good, the effect was good, or vice-versa. The treatment effect of two PD patients invalid to levodopa was not good in this study. Therefore, when choosing the transplantation indications, we should pay attention to this point.

Because of the low antigenicity of neural stem cells, we did not observe immunological rejection before or after operation, even we did not use immunosuppressant. A few patients had short-time postoperative hemiparesis and salivation, leaving no physical dis-

abilities. So, the brain transplantation of neural stem cells in the treatment of PD is safe and efficient.

Conclusion

The therapy, computer assisted stereotactic transplantation of human neural stem cells in the treatment of PD, is safe and efficient.

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Volume 2 Issue 8 November 2018