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Xiaoling Guo  
Department of Neurology, The 981st Hospital of the Chinese People's Liberation Army, Chengde 067000, Hebei, China

Xin Wang  
Department of Neurology, The 981st Hospital of the Chinese People's Liberation Army, Chengde 067000, Hebei, China Chengde Medical University, Chengde 067000, Hebei, China

Yan Li  
Department of Neurology, The 981st Hospital of the Chinese People's Liberation Army, Chengde 067000, Hebei, China

Bo Zhou  
Department of Neurology, The 981st Hospital of the Chinese People's Liberation Army, Chengde 067000, Hebei, China Chengde Medical University, Chengde 067000, Hebei, China

Weidong Chen  
Otorhinolaryngology Department, The 981st Hospital of the Chinese People's Liberation Army, Chengde 067000, Hebei, China

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Olfactory ensheathing cell transplantation improving cerebral infarction sequela: a case report and literature review

Xiaoling Guo1 (✉), Xin Wang1,2, Yan Li1, Bo Zhou1,2, Weidong Chen3, Lihua Ren3

1 Department of Neurology, The 981st Hospital of the Chinese People’s Liberation Army, Chengde 067000, Hebei, China
2 Chengde Medical University, Chengde 067000, Hebei, China
3 Otorhinolaryngology Department, The 981st Hospital of the Chinese People’s Liberation Army, Chengde 067000, Hebei, China

ABSTRACT

Stroke is the second leading cause of death and the main cause of long-term disability in the world. Therefore, treatment of the sequelae of stroke is one of the most important challenges in clinical neurotherapy. A 63-year-old Chinese woman with inarticulateness and right limb physical activity disorder for more than 4 months received olfactory ensheathing cells (OECs)-based neurorestorative therapy during the stay in hospital. Her neurological functions improved during 1-year follow-up. This case report showed that OECs therapy could be a treatment option for cerebral infarction sequela.

1 Background

Stroke is the second leading cause of death and the main cause of long-term disability with 6.24 million death cases every year in the world [1]. Currently, there are only two FDA-approved treatments for ischemic stroke: tissue plasminogen activator intravenous thrombolysis and stent-assisted thrombectomy [2]. However, they can only be used in patients with hyperacute ischemic stroke, thus only a relatively small group of patients have chances to receive timely and effective treatments. Besides, stroke has a mortality of more than a quarter and a poor prognosis with a permanent disability of 40% [1]. Treatments, nursing and long-term rehabilitation impose heavy burdens on patients and their families.

In recent years, cell transplantations have been showed of great therapeutic potential in neurorestoration. A number of studies have demonstrated that olfactory ensheathing cells (OECs) function in secretory [3, 4], tissue remodeling [5], tissue migration [6–8] and immune regulation [8, 9], and are prominent in repairing various nervous system diseases. In particular, OECs have eminent ability to stimulate axonal repair, enhance plasticity and support axonal retention in the central nervous system (CNS) [10]. OECs could be one of the potential candidates of cell transplant strategies to repair CNS diseases [11]. The following case report of OECs nasal submucosal transplantation improving cerebral infarction sequela in our hospital will provide a novel therapeutic option for patient with similar conditions.

2 Case report

2.1 General information

The 63 years old female patient, who was admitted to
our hospital because of “inarticulateness and right limb physical activity disorder for more than 4 months”, was suddenly found to have inarticulateness, unclear pronunciation, incomprehensible expression and the right limb physical activity disorder 4 months ago, and was diagnosed as “acute cerebral infarction” and “hypertension level 3 (very high added risk)” by local hospital in January 2017.

After arterial thrombectomy, anti-platelet aggregation and rehabilitation treatments, the clinical symptoms were improved. Unfortunately, the right upper extremity of the patient could only be lifted slightly with an incapacitated right hand. The patient could only walk on crutches due to right lower extremity muscle weakness, and inarticulateness and expression disorder symptoms still existed.

The patient had a history of hypertension for three years and the systolic blood pressure could reach 220 mmHg, but the blood pressure was basically well controlled through long-term regular medication.

Clinical examinations showed that the patient was conscious, ataxic aphasia, right central facial-lingual paralysis, right side of the body hypoalgesia. The right upper limb proximal muscle strength was level 3, distal muscle strength was level 0, right lower limb muscle strength was level 4+. The muscle tension was slightly higher, the right limb tendon reflex was (+++), the left limb tendon reflex was (++), and right bilateral Babinski sign was positive.

The magnetic resonance imaging (MRI) of brain (01/04/2017) showed patchy long T1 and long T2 signal in the left frontal white matter, left basal ganglia and left temporal-occipital-parietal junction. The magnetic resonance angiography (MRA) (01/04/2017) showed the vessel walls in intracranial segment of bilateral internal carotid artery, bilateral middle cerebral artery and anterior cerebral artery were rough. The M2 segment (insula segment) of the left middle cerebral artery was slender (Fig. 1). The admission diagnoses were “hypertension grade 3 (very high added risk) and sequelae of cerebral infarction”.

2.2 Ethic

The patient was fully informed and signed the informed consent for the treatment. The clinical research program and agreement were approved by Neurorestoratology Professional Committee of Chinese Medical Doctor Association and Research Ethics Committee of 981 Hospital of the Joint Logistics Support Force of the Chinese People’s Liberation Army (the 266 Hospital of PLA).

2.3 Interventions, transplanted cell acquisition and preparation

OECs were obtained from donated aborted embryo (3 to 4 months, pregnant women and their family members have signed informed consent) from cooperative hospitals, and were prepared and identified in accordance with literature [12] (Fig. 2).

2.4 Cell transplantation

After admission, antiplatelet aggregation, statins and other drugs were given symptomatically, and subsequently rehabilitation treatments were used. At 07/05/2018, 5 × 10⁶ (0.3 mL)/side of OECs were injected into bilateral nasal olfactory submucosa (Fig. 3).

2.5 Follow-up

The patient was follow-up by assessment of muscle strength measurement, National Institute of Health...
Stroke Scale (NIHSS), the Modified Rankin Score, Barthel Index Score and modified Ashworth Score at before treatment, and 1 month, 3 months, 6 months, 1 year after treatment. And MRI were done 1 year after treatment.

### 3 Results

Before treatment, the patient had inarticulateness, unclear pronunciation and incomprehensible expression. 1 month after treatment, although the patient still had inarticulateness, her pronunciation was improved and others could understand the semantics. 3 and 6 months after treatment, the patient was not fluent in speech, spoke slowly and communicated with others normally. One year after treatment, the patient was basically fluent in speech, spoke slowly and communicated with others normally. Specific muscle strength and various neurological function scores were shown in Table 1 and Table 2. After one year, the NIHSS score was 5 (face 2, speech 1, movement 1, feeling 1). The reviewed MRI at 20/04/2018 showed patchy long T1 and long T2 signal in left basal ganglia and left temporal-occipital junction (Fig. 4).

### 4 Discussion

In recent decades, due to the rapid development of science and technology, ultra-early imaging diagnosis is guiding the active treatments of ischemic stroke and the subsequent secondary preventions are gradually standardized, so that the mortality caused by cerebrovascular disease is gradually reduced. However, stroke remains the leading cause of death and long-term disability worldwide [13]. The occurrence of stroke is accompanied by many pathophysiological processes such as inflammation, endothelial dysfunction, thrombosis and oxidative stress. The known risk factors cannot fully explain the accurate pathological mechanism of stroke, nor they can fully explain the adverse prognosis of stroke [14]. Generally, 80% stroke cases are ischemic stroke [15]. Ischemic events trigger complex molecular cascade reactions, including cell depolarization, excitotoxicity, impaired cellular energy metabolism, and disruption of the blood-brain-barrier [3]. Current treatments of ischemic stroke are limited to restore perfusion, promote circulation and protect cells from acute death [16]. Therefore, functional neurological recovery in the subacute and chronic phases of ischemic stroke remains one of the most challenging tasks in clinical neurorestorative practice [17].

<table>
<thead>
<tr>
<th>Muscle strength (level)</th>
<th>Before treatment</th>
<th>1 month after treatment</th>
<th>3 months after treatment</th>
<th>6 months after treatment</th>
<th>1 year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proxima of right upper limb</td>
<td>3</td>
<td>3</td>
<td>3+</td>
<td>4—</td>
<td>4+</td>
</tr>
<tr>
<td>Distal of right upper limb</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Right lower limb</td>
<td>4—</td>
<td>4</td>
<td>4</td>
<td>4+</td>
<td>4+</td>
</tr>
</tbody>
</table>

| Table 1 The results of muscle strength measurement. |

<table>
<thead>
<tr>
<th>NIHSS (score)</th>
<th>Before treatment</th>
<th>1 month after treatment</th>
<th>3 months after treatment</th>
<th>6 months after treatment</th>
<th>1 year after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Score (score)</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Barthel Index Score (score)</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Modified Ashworth Score (level)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| Table 2 The results of NIHSS, Modified Rankin Score, Barthel Index Score and Modified Ashworth Score. |
OECs, special glial cells originated in the nasal mucosa, are distributed in the first, second and olfactory nerves of the olfactory bulb, envelop the olfactory nerve bundle into the olfactory bulb, wrap the olfactory nerves and enter into brain with the olfactory axons. OECs help to separate olfactory axons from other cells in brain. OECs can induce the olfactory nerve to enter the central nerve system. Therefore, the olfactory nerve has excellent regenerative ability and could renew consecutively. The regenerated axons could grow through the border between peripheral and central nerve system, build synaptic connections with the olfactory bulb. This process is repeated once every 1 to 2 months. This particular glial cell is an external condition and plays an important role in central nerve system regeneration [18, 19]. Many molecules (NCAM, L1, N-cadherin) [20] related to cell adhesion and axon growth are expressed on OECs membrane, support and promote the growth and survival of neurons, improve the microenvironment in damaged CNS tissues, activate resting axons and neurons, restore nerve conduction, promote axonal regeneration and myelination repair, and restore some of the lost nerve function [21]. OECs also secrete soluble factors that promote neural differentiation and neurite elongation. Secreted matrix metalloproteinase 2 (MMP2), sonic hedgehog protein (Shh), laminin and fibronectin could induce neural progenitor cells to differentiate into neurons, regulate neural cells migration and differentiation in different tissues in the body. OECs direct olfactory axons from the nasal olfactory mucosa to the olfactory bulb, connect the peripheral nervous system (PNS) and the CNS, support the continuous renewal of olfactory neurons in the olfactory system and stimulate axonal repair and functional recovery [22]. Due to the strong axonal outgrowth guiding ability of OECs, increasing evidence showed that OECs have therapeutic potential in neurorestorative therapy [23]. Studies have confirmed that OECs have neurorestorative properties in animal stroke model. Transplanted OECs have been reported to survive for over 8 weeks and could migrate to infarcted tissue and long distances along the white matter. It can increase white matter markers, reduce lesion volume and improve neurological score [16]. Human OECs have been observed to significantly improve neural function and promote neuroplasticity in the ischemic brain of rats and mice [17].

In recent years, cell therapy has been proven to be a promising clinical treatment option for CNS diseases or injuries [24]. OECs transplantation has become a hotspot in the field of Neurorestoratology. It is one of the most potential therapeutic methods of CNS diseases. Its clinical applications have been carried out in many medical research centers [25–28]. In this case, although the patient received timely arterial thrombectomy after the onset of stroke, the neurological impairment remained. The dysfunction did not improve in the following 4 months after stroke.

After 1 year’s follow-up, the language function improved 1 month after treatment, while did not improve in the golden recovery period of 3 months after stroke. The muscle strength of the right lower limb improved one month after treatment and the muscle strength of the right upper limb improved significantly 3 months after treatment. Specially, the muscle strength of distal right upper limb recovered from level 0 to 2 in the third month and reached 4 at 1 year after treatment. The NIHSS score decreased from 10 to 7 before treatment. Modified Rankin Score decreased from 4 to 2. The Barthel Index Score increased from 60 to 90, daily life was basically on its own, which greatly reduced the burden of the family economy and nursing. Although muscle tension was improved, there was no significant change in the Modified Ashworth Score, which may be related to the less degree of dystonia itself. This is the first clinical case report of OECs-based neurorestorative therapy treating a cerebral infarction sequela patient by nasal olfactory submucosal transplantation, which shows some promising results.
5 Conclusion

The treatment results in this case suggest that OECs transplantation may be a selective or alternative therapy to improve the sequelae of stroke. However, multi-center larger sample clinical trials are still needed. The combination of multiple cell and multiple pathway intervention strategies may have great potential to improve or restore neurological functions in CNS diseases and damage in the future.

Disclosure

The authors report no conflicts of interest in this work.

References


Xiaoling Guo, professor, vice president and director of the Brain Center of The 981st Hospital of the Chinese People’s Liberation Army Joint Logistics Support Force. She is the standing committee member of the Neurorestoratology Professional Committee of CMDA and deputy editor-in-chief of Hebei Medical Journal. She focuses on stroke nerve repair and molecular pathological mechanism of spinal cord injury. Email: gxl266@sina.com.

Xin Wang, PhD candidate, Department of Brain Center, The 981st Hospital of the Chinese People’s Liberation Army Joint Logistics Support Force. She is a graduate student of Chengde Medical University, and has published 4 SCI articles under the guidance of her mentor professor Xiaoling Guo. Email: sndwxy@sina.com.

Yan Li, PhD, Department of Brain Center, The 981st Hospital of the Chinese People’s Liberation Army Joint Logistics Support Force. She focuses on stroke nerve repair and rehabilitation of nervous system diseases. Email: 1106970200@qq.com.

Bo Zhou, PhD candidate, Department of Brain Center, The 981st Hospital of the Chinese People’s Liberation Army Joint Logistics Support Force. She is a graduate student of Chengde Medical University, and has published 2 articles under the guidance of her mentor professor Xiaoling Guo. Email: 18244571311@163.com.
Weidong Chen, Deputy director of otolaryngology, The 981st hospital of the Chinese people’s Liberation Army Joint Logistics Support Force. Email: chendong.dong@163.com.

Lihua Ren, Deputy director of otolaryngology, The 981st hospital of the Chinese people’s Liberation Army Joint Logistics Support Force. Email: renlh158@163.com.