

OLFACTORY ENSHEATHING CELLS IN THE TREATMENT OF THE TETHERED CORD SYNDROME: CASE REPORT

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There are several data and commentaries regarding the role of the stem cells as effective therapies in the treatment of the central nervous system's lesions. Even if at the experimental level there have been reported very promising results, when these methods have been applied in clinical field the results were not very successful. In this context, the numerous reports about patients with significant improvement of the neurological status after stem cells inoculation or olfactory ensheathing cells (OECs) inoculation performed by the researchers from Beijing Xishan Hospital, Beijing, China, adds a discordant note in this general pessimist background. Therefore, we will present the original discharge letter from the Beijing Xishan Hospital, Beijing, China then we will make some commentaries and will draw the final conclusions.

Keywords: olfactory ensheating cells, tethered cord, myelo-meningocelle

CASE REPORT

Patient presentation:

A 5-year-5-month-old girl from Romania, was admitted to Beijing Xishan Hospital, Beijing, China on November 7, 2007 with 5 years history of paraplegia, urinary and bowel movement incontinence due to a meningomyelocele accompany with hydrocephalus. He underwent neoplasty of meningomyelocele and ventriculo-peritoneal shunt on right side three months after her born. After operation, she was not able to move her legs and the feeling in her legs almost disappeared. Severe scoliosis was noticed. Urinary and bowel movement was incontinence. She was able to sit and crawl by herself. Her intelligence development was normal. She went to school followed with study well.

Admission diagnosis: Tethered Cord Syndrome

Physical Examination:

Motor: Upper extremities were 5/5 bilaterally; Lower

extremities: Hip flexors was 2/5 on the right, 3/5 on the left; Knee extensors, Ankle dorsiflexors, Ankle plantar flexors and Long toe extensors were 0/5 bilaterally. Sensation: Light touch decreased at L1-2 on the right, at L1-L3 on the left and disappeared from L3 on the right, from L4 on the left. Muscular tension in her legs was mildly decreased. Moderate atrophy was noticed and hyporeflexia could be found in her legs. Pathologic reflex were negative bilaterally. Severe scoliosis was noticed. She was not able to perform heel-to-shin examination.

Preoperator Score:

- ASIA motor score was 27 points on the right, left 28 points
- ASIA light touch score was 40 points on the right, left 41 points
- ASIA pin prick score was 38 points on the right,

left 42 points

- Score of Xishan Hospital Spinal Cord Injury Functional Rating Scale was 24 points

Operation Procedure:

Following the procedure of cell HLA-matching between the donor and recipient, under general anesthesia, the surgical transplantation of olfactory ensheathing cells was done on November 12, 2007. 100 microl containing about 1 million cells were injected into the spinal cord conus of the patient. At the same time the Surgical Lysis of Tethered Cord was done at the segments at L4

Post-Operative Course

She was treated by the adjunct regimens including the massage, physical therapy and acupuncture therapy during the whole admission. When the patient discharged, neurological functional improvement was found. She felt that the sensation low down and the muscular power of her legs increase. Also the sweating on her legs were found, while before not. Motor: Upper extremities were 5/5 bilaterally; Lower extremities: Hip dorsiflexors, Ankle plantar flexors and Long toe extensors were 0/5 bilaterally. Sensation: Light touch decreased at L2-3 on the right, at L2-L4 on the left and disappeared from L4 on the right, from L5 on the left. Pin prick decreased at L2 on the right, at L2-L3 on the left and disappeared from L3 on the right, from L4 on the left. As her incision has not healed completely due to its edges located in the skin part were not well. So she needed to keep lying on the bed, if possible lying on the stomach is the best. She should let the incision be pressed with bandage which was aseptic all the time, till it cured well. But don't press the incision hardly in order not to pierce it in case of infection.

Postoperative Score:

- ASIA motor score was 28 points on the right, left 29 point

- ASIA light touch score was 41 points on the right, left 42 points.

- ASIA pin prick score was 41 points on the right, left 42 points.

- Score of Xishan Hospital Spinal Cord Injury Functional Rating Scale was 25 points, which increased by 1 point than before including the aspect of sweating.

Discharge Order

1. Please require the local surgeon check the incision carefully every three days. If they have some questions about the incision, please let them inform us.

2. The patient should get plenty of suitable and soft standardized exercise.

3. She should let the incision be pressed with bandage all the time, till it cured well. But don't press it too much in order to keep it blocking. If the cut can not cure and open, she had better to take the skin flap transplantation.

4. Don't get up and sit and keep lying on the bed, if possible lying on the stomach is the best.

5. Don't pierce the incision blocking.

6. After returning home, the patient was required to be followed up by her primary care physician and her family. She will undergo checkups at interval of 1 month, 2 months, 3 months, 6 months, 1 year, 2 year, and 5 years. These checkups must include the evaluation completed by the physician or patient's family.

DISCUSSIONS

Objective of this paper is to compare findings of a patient with clinical complete tethered cord syndrome before and after receiving olfactory ensheathing cellular implants.

No improvement in sensory function, motor function, and other functional amelioration could be observed after the injection of olfactory ensheathing cells (OECs).

The neurosurgical procedure lead postoperatively to unhealed incision and it will need aseptic bandages all the time, till it will cure well.

We can consider that the period after surgery is too short for a correct assessment.

Also in this case, the neurosurgeon will obtain his follow up about the injection of olfactory ensheathing cells (OECs) into the spinal cord for tethered cord by e-mail: „the patient will be followed up by her primary care physician and she will undergo checkups at interval of 1 month, 2 months, 3 months, 6 months, 1 year, 2 year, and 5 years. These checkups must include the evaluation completed by the physician or

patient's family". We consider that the neurological examinations must be associated with MRI examination; MRI will be used as a spinal cord lesion assessment tool before and after the surgical procedure. (3)

The risk of foetal olfactory ensheathing cells transplant is an immune rejection and it could compromise the effectiveness of the transplanted cells. There are enough studies about autologous transplantation of olfactory ensheathing cells into the spinal cord, after nasal biopsy and olfactory ensheathing cell culture. (5)

There are a lot of data about the cells therapies in the treatment of the central nervous system's lesions. Stem cells are feasible candidates for cell therapy of spinal cord's lesions. Different therapeutic strategies based on stem cells have been developed and studied. Several strategies support cell replacement of the damaged tissue while others rely on therapeutic effects induced by cell transplantation. There are no fully restorative treatments for spinal cord lesions, but various rehabilitative therapies have been tested in animal models. Several researcher groups have tried to transplante stem cells or other types of cells into human with chronic spinal cord lesions. The preliminary reports showed modest improvements but the peer-reviewed results have not yet been reported. (6)

The olfactory nerve is the only part of the central nervous system that is known to regenerate continuously throughout adult life. It is thought that the ability of the olfactory nerve to regenerate continuously is assigned to the presence of olfactory ensheathing cells (OECs). Olfactory ensheathing cells are specialised glial cells that surround the olfactory sensory axons in the nose. They have properties of Schwann cells in promoting and assisting growth of axons. They are unique among the glia in residing both inside and outside the central nervous system, in the olfactory bulb and olfactory nerve, respectively (5).

The olfactory ensheathing cell (OEC) has attracted much interest recently because of its potential for transplantation-based therapy of CNS disease. Rat OECs are able to remyelinate demyelinated axons and support regeneration of damaged axons. (1)

These properties have led to an increasing use of olfactory ensheathing cells in preclinical models of transplantation for spinal cord repair including complete transection, hemisection, tract lesion, and contusion with over 50 studies published in the last years.

Olfactory ensheathing cells and stem cells are different.

There is a difference of the pathophysiology between the tethered cord syndrome with paraplegia, urinary and bowel movement incontinence and the traumatic spinal cord injury. During the spinal cord injury there is a complete or an incomplete section; therefore there is a disrupted spinal cord or some types of contusion, compression, penetration or laceration of the spinal cord. Spinal cord injury leads to the death of cells, including neurons, oligodendrocytes, astrocytes and precursor cells, and any resulting cavities and cysts may interrupt descending and ascending axonal tracts, although circumferential white matter is often spared. After the initial insult to the spinal cord, additional structure and function are lost through active secondary processes (ongoing apoptosis of oligodendrocytes and loss of myelin). Demyelinated axons are observed up to a decade after human spinal cord injury, and the extent to which these axons survive unmyelinated or become remyelinated by central or peripheral myelin is very important for spinal cord.



FIG. 1A CT image of a left acute extradural hematoma - [male patient , 43 years old , GCS = 6]

OLFACTORY ENSHEATHING CELLS

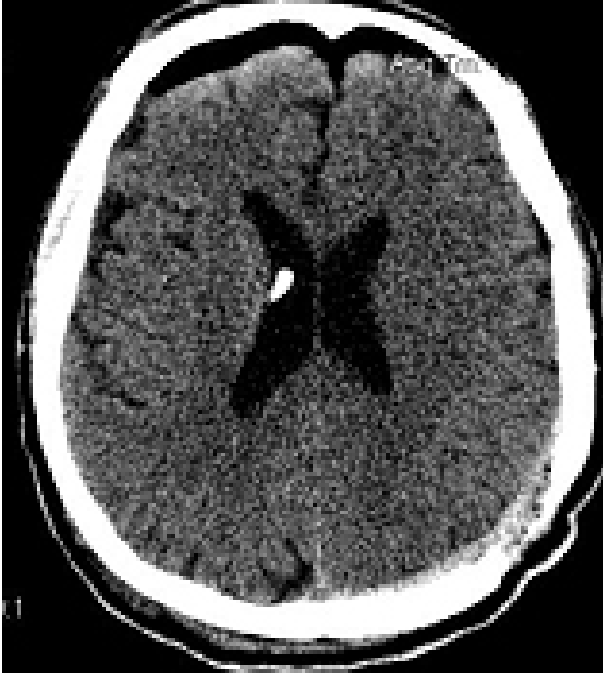


FIG. 1B The same case: ICP monitoring after surgery

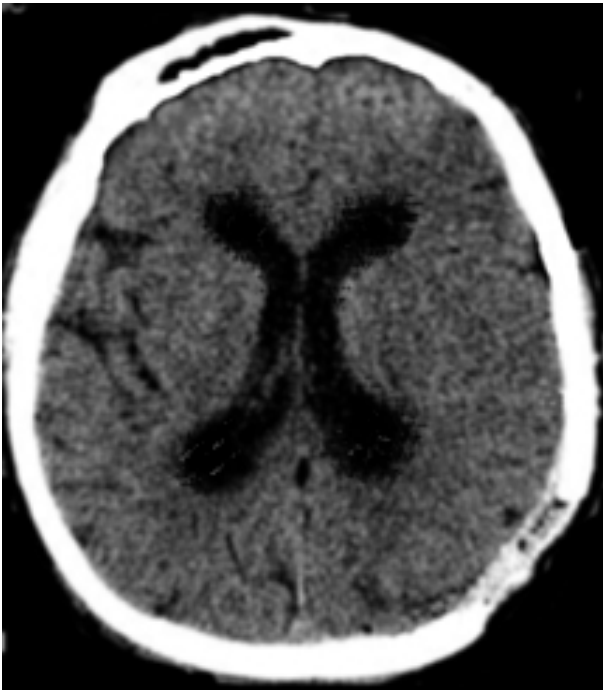


FIG. 1C Post - traumatic hydrocephalus occurs four months after traumatic brain injury

When the spinal cord is tethered, this abnormal stretching puts tension on the cord and

there are a maldevelopment of the nerves that control the legs, feet, bowel and bladder.

Therefore there are a ageneses of the conus medullaris and of the cauda equina, also of the lumbar and sacral nerves.

Several clinical trials worldwide have been initiated that use transplantation of olfactory tissue containing OECs into the damaged spinal cord of humans. The olfactory ensheathing cells (OECs) inoculation in the scar of the traumatic spinal cord injury has the purpose to induce remyelination at this level, as well as to allow for regeneration in specific circumstances and transplanted Schwann cells (SCs) share these repair properties too. (7) Specifically, OECs promote axon regeneration and functional recovery indirectly by augmenting the endogenous capacity of host Schwann cells to invade the damaged spinal cord. Together with Schwann cells, OECs create a 3-dimensional matrix that provides a permissive microenvironment for successful axon regeneration in the adult mammalian central nervous system. (2)

Theoretically the olfactory ensheathing cells (OECs) inoculation in tethered cord can not regenerate the neurons of the agenesed conus medullaris; olfactory ensheathing cells (OECs) inoculation will permit only an axon regeneration if prior to this there were functional neurons and functional axons. Therefore the use of olfactory ensheathing cells is used for regrowth of lesioned axon projections and restoration of neuronal connectivity. (8)

The Chinese neurosurgeons have performed olfactory ensheathing cellular transplants from aborted fetuses in more than 400 patients with SCI and 100 patients with amyotrophic lateral sclerosis (ALS) at Xishan hospital, Beijing. They extract OECs from fetal olfactory bulb tissue. After cultivation and purification of the cells (a 10 to 14 days process), they obtain a "clinical standard OECs" that can be used for the surgery.

They have treated patients with different CNS diseases, such as amyotrophic lateral sclerosis, spinal cord injury, multiple sclerosis, Friedreich's ataxia, cerebral palsy, brain trauma, spinal muscular atrophy,

persistent vegetable status, sequela of stroke, dementia, hereditary spastic paraparesis, myelitis etc. Therefore the olfactory ensheathing cellular transplants were used in a various CNS diseases, with different pathophysiology and without clear inclusion criteria into clinical trials.

The search for new therapies must be based on scientific methods. Patients must meet a specified criteria for entry in a scientific trial, are randomly assigned to one of two treatments, are carefully examined for the duration of the likely benefit of the experimental and other intervention, and are examined at the end of the trial by physicians who do not know which treatment was given (4).

CONCLUSIONS

1. Based on the observation of this case and on other series of presented operated subjects, the efficacy of olfactory ensheathing cells implantation procedure are unclear.

2. In this case the period after surgery is too short for a correct assessment.

3. There are numerous articles that show the transplanted olfactory ensheathing cells are able to remyelinate demyelinated axons into the traumatic spinal cord injury. There is a difference of the pathophysiology between the tethered cord syndrome and the traumatic spinal cord injury

4. Most of researchers prefer autologous transplantation of olfactory ensheathing cells into the

spinal cord, after nasal biopsy and olfactory ensheathing cell culture.

5. In China the olfactory ensheathing cellular transplants were performed in various CNS diseases, with different pathophysiological mechanisms and without clear inclusion criteria into clinical trials.

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