

Two cases of bone marrow tissue implant into chronic cervical spinal cord injury

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Abstract

Two patients with chronic cervical spinal cord injury and quadriplegia underwent partial resection of the medular scar and implant of bone marrow tissue with a combination of drugs at the site of spinal cord injury. Post-operatively they received a similar treatment in the neuromotor rehabilitation centre and were treated additionally with cerebrolysin. Sensory improvements were noticed, but no significant motor improvements were observed twenty months afterwards.

Keywords: autologous bone marrow implant, sensory recovery, spinal cord injury, spinal scar

Spinal cord injury (SCI) is a major medical problem worldwide and cervical spinal cord injuries can lead to quadriplegia and have devastating consequences for victims, families, and society in general. Today there are no fully restorative treatments for spinal cord injury, but various cellular therapies have been tested in animal models. 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 occur. Spinal cord injury culminates in glial scarring, a multifactorial process that involves reactive astrocytes, microglia and macrophages, fibroblasts and Schwann cells.(3,4,8,9)

The scar is often oriented perpendicularly to the neuraxis and appears impenetrable. The scar also contains molecular inhibitors of axon growth. Progressive expansion of the injury across more than one segment can also occur over months or years. Therefore after spinal cord injury there are two types of lesions : complete disruption of the spinal cord or different types of scars.

The scar of the spinal cord can be:

- a complete and impenetrable glial scar on the site of spinal cord injury,
- an incomplete scar and a post-traumatic syringomyelia or post-traumatic cysts on the site of spinal cord injury,
- a filiform connective scar of the two segments of damaged spinal cord.

The glial scar, which is rich in growth inhibitors, as chondroitin sulfate proteoglycan (CSPG), is a major impediment to axonal regeneration following injury.

The inability to repair spinal cord damage is attributed to several factors:

- the presence of inhibitory substances in the tissue that surrounds the lesion,
- changes inside adult nerve fibres that make them unable to respond well to growth-inducing signals,
- the formation of cysts at the injury site which growing fibres cannot cross,
- the lack of nerve growth factors at the injury site,
- the formation of scar tissue at the injury site with additional inhibitory substances.

Therefore any treatment must solve the above difficult problems.(7,13,14)

There are no fully restorative treatments for spinal cord injury, but various rehabilitative therapies have been tested on animal models to improve functional outcomes after spinal cord injury. The stem cells based therapies are being tried in order to repair or replace tissues or cells damaged by injuries or diseases and to treat serious chronic diseases, such as spinal cord injuries.

Three therapeutic concepts are currently being envisaged:

1. Transplantation of differentiated cells derived from stem cells. The source for the specific differentiated cell types could be embryonic or somatic stem cells including the patient's own stem cells.

2. Direct administration of stem cells directly to the patient; the stem cells will differentiate into the desired cell type .

3. Stimulation of endogenous stem cells, induced by stimulating an individual's own population of stem cells by administrating growth factors.

Stem cells are feasible candidates for cell therapy of spinal cord injury. (8,10,15) Bone marrow cells are the subject of

extensive interest because of their stem cell like characteristics and pluripotency. (11,16,18)

There are more data supporting the beneficial effects of bone marrow cells in SCI:

1. bone marrow contains multipotent adult progenitor cells that produce a variety of cell types, including neuroectodermal, mesodermal and endodermal cell types.

2. bone marrow cell transplants improve function recovery and differentiate into astrocytes, oligodendroglia and neural presursors in animal experiments.

3. bone marrow cell transplants facilitate remyelination of the spinal cord, appear to be neuroprotective and also promote regeneration in injured animal spinal cords. (21,22,24,25)

Neurotrophins and growth factors play an important role in development of the central nervous system and several neurotrophic factors induce neuroprotection in traumatic spinal cord injuries. (20) Understanding the mechanisms by which adult stem cells produce growth factors and the effect of components of the spinal cord injury milieu to stimulate growth factor production and to promote spinal cord lesion repair are very significant issues.

A combination of stem cells therapy with neurotrophins is a novel aspect of treatment in spinal cord injury and it will attenuate the neurological damage and could help restore the normal function of spinal cord.

There are several similarities between the traumatic brain injuries and spinal cord injuries and there are also some similarities between the both their treatments. Numerous studies have documented the neuroprotective and neurotrophic

properties of cerebrolysin in traumatic brain injury. Cerebrolysin is a standardized porcine brain-derived drug and it can pass through the blood-brain barrier.

This paper presents the experience of two patients with traumatic chronic cervical spinal cord injuries with quadriplegia and the results of the microsurgical resection of the spinal scar and the implant of bone-marrow tissue in the site of the spinal cord lesion .

Methods

Two patients with chronic cervical spinal cord injury and quadriplegia voluntarily participated in this study. The cervical SCI events occurred at least two years before this study. Two physicians independently assessed the neurological injury status of each patient before and at regular intervals after the surgery. The surgical approaches and the implant were performed by the same neurosurgical team. The study protocol was approved by the Ethics Committee of the Hospital “Prof Dr Nicolae Oblu“, Iasi and the subjects gave informed consent.

Each patient underwent a cervical laminectomy to expose the site of the cervical spinal cord injury and a microsurgical partial resection of the medular scar and implant of autologous bone marrow tissue with a combination of drugs at the site of spinal cord injury. (Figure 1) No post- surgery complications occurred.

Post-operatively the patients received a similar treatment in the neuromotor rehabilitation centre, also they received 5 - 10 mL/day for three to five months postoperatively.

Results

Two male patients were included in this study with the age of 26 and 33 years. Sensory improvements were noticed, but no significant motor improvements were observed twenty months afterwards. (Table 1).

Discussion

The mechanisms of spinal injury are very important for the type of lesion of the spinal cord. When the spinal cord is injured, a number of events occur : injury of the neurons (broken neural cell membranes, cut axons), blood vessels disruption, bleeding in the central grey matter, spinal cord edema and hypoperfusion of the spinal cord, the dura mater injury. The spinal cord injury is a complete lesion - a disrupted spinal cord, or an incomplete lesion - different types of compression or laceration of the spinal cord. A dura mater sheath lesion is followed by a fibroblastic reaction in the epidural tissue extended into the spinal cord with a connective scar, but maintaining the dural continuity can limit the formation of connective tissue scarring in the epidural space. (7)

No case	Age F/M	Cervical SCI level	History of injury	Neurology	Cerebrolysin postoperatively	Outcome (m = months)
1	26/M	C4-C5	3y	quadriplegia	Yes ; 5 mL/day 3 months	20 m : C7
2	33/M	C5-C6	3y	quadriplegia	Yes ; 5 mL/day 3 months	22 m : C8

The dural duraplasty following acute spinal cord laceration may improve cerebrospinal fluid flow by limiting meningeal fibrosis adjacent to the injury and minimize connective tissue scar formation. (9)

The surgical treatment (ideally - within eight hours of the injury occurring) must remove the tissues causing spinal cord compression, must correct a gross misalignment and must stabilize the spine. Immediate surgery for spinal decompression including the duraplasty is of high importance for the prognosis and evolution of spinal cord injury.

The secondary spinal cord injury is the damage that continues in the hours following trauma and consists of reduction in blood flow at the level of injury, excessive release of neurotransmitters (glutamate), inflammatory response, free radicals attack neurons and neuronal apoptosis. During this delayed secondary spinal cord injury the treatment may reduce the extent of disability, eg. methylprednisolone given within 8 hours of the injury occurring significantly improves recovery in humans. (2, 7,18,19)

An efficient treatment in spinal cord lesions must combine several main approaches:

- minimising the initial damage and protecting surviving neurons - neuroprotection,
- removing barriers: after the injury the scar tissue gradually fills the damaged area and it is an impenetrable barrier and it does not allow regenerating nerve fibres to pass through.
- blocking factors which inhibit neural regeneration,
- modulation of inflammatory response following spinal cord injury,

- preventing inhibition of regrowth,
- tissue engineering: biocompatible materials can form a bridge across the damaged region ,
- stimulating and guiding – neurotrophic factors,
- replacing damaged cells – stem cells therapy,
- correctly reconnecting the damaged neural circuits inside and outside the spinal cord

Many researchers have tried to find effective strategies to improve outcomes after spinal cord injuries.(2,7,14,27,28)

Substances that limit secondary injury processes and promote repair and regeneration of the injured spinal cord such as monosialotetrahexosylganglioside (GM-1), 4-aminopyridine (4-AP), [a potassium-channel blocking agent], brain derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF), also inhibitors of Nogo (neurite outgrowth inhibitor) and MAG (myelin-associated glycoprotein), have been studied. Also transplanted tissues and cells, such as blood macrophages, bone marrow transplant with GM-CSF, olfactory ensheathing cells, fetal tissues, stem or progenitor cells, appear to produce neurological improvements.(11,29)

In pathological conditions eg. spinal cord injury, the neurotrophins promote survival and rescue nerve cells from death and promote neurite extension, neuronal survival and differentiation. In spinal cord injury, the neurotrophins are able to enhance axonal regeneration and reduce paraplegia. (23,24,25,26) Some authors showed that the most efficient strategy for the acute complete transection of spinal cord was a combination of implantation of Schwann cells, plus neuroprotective agents and growth factors administered in various

ways, olfactory ensheathing cell (OEC) implantation and chondroitinase administration.(2,3) Other study concluded that combinations of interventions were needed to surmount the multiple barriers to recovery in spinal cord injury recovery.(20) Two small studies noted sensory improvements in SCI patients who underwent autologous bone marrow cell transplantation (BMT) in conjunction with granulocyte macrophage-colony stimulating factor (GM-CSF) administration. (12,17)

Our study included two complete cervical SCI patients and bone-marrow tissue obtained from the patient was implanted in conjunction with cerebrolysin as neurotrophic factor. The surgical procedure consisted of microsurgical dissection and partial removal of the spinal cord scar and implanting of the bone-marrow tissue into the spinal cord injury site. Sensory improvements were noticed, but no motor improvements were observed twenty months afterwards. There are only few studies of the effect of cerebrolysin in nerve and spinal cord injuries in animal models (1,5,6) and a comparison of the efficacy of brain-derived neurotrophic factor (BDNF) and cerebrolysin treatment demonstrated that BDNF has more modest effects in functional recovery than cerebrolysin in nerve injury.(6) Our results show that the cerebrolysin acted as a neurotrophic factor after the bone marrow implant and it was clinically effective in the long term treatment of one patient with chronic traumatic spinal cord injury.

Conclusion

This is a preliminary study of the autologous bone marrow tissue implant into the lesioned cervical spinal cord and there are only two cases, but it is the first

study about cerebrolysin in human cases of traumatic chronic cervical spinal cord injury. The bone-marrow tissue transplantation procedure has no complications. The post - injury scar's microsurgical partial removal may make the injury site more permeable to the axons attempting to re-grow through. This result is promising, but much follow-up work is needed to document the long-term benefits.

The results are modest - like everywhere else, yet - but promising, compared to the lack of any effective therapeutic alternative.

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