

Review Article

Treatment of multiple system atrophy - the past, present and future

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Abstract: Multiple system atrophy is a sporadic progressive degenerative disease which is characterized by multiple central nervous systems involved. So far, there is no effective medicine to cure MSA. The main research direction of treatment includes immunization transplantation and cytotherapy. Human umbilical cord blood is the residue of blood in the placenta and umbilical cord after fetal delivery. It is the most abundant cell bank and its usage is not limited to treat hematological diseases. The researches about hUCB-MNC treatment on MSA are increasing gradually. The potential of other MSC is also discussed. Lateral atlanto-occipital space puncture is an ingenious way created by Professor Dianrong Gong. More than 30 cases of MSA have been treated by this method with fine clinical effect and without serious complications. It indicates that stem cells treatment is a valid method for refractory nerve system diseases.

Keywords: Multiple system atrophy, lateral atlanto-occipital space puncture, stem cells, human umbilical cord blood-mononuclear cell

Multiple system atrophy (MSA), also named Parkinsonism plus syndrome in the past, is a sporadic progressive degenerative disease which is characterized by multiple central nervous systems involved [1]. Epidemiologic data showed the MSA morbidity is 0.60-3.00/100,000 per year, and the prevalence rate is 1.90-4.90/100,000 per year [2, 3]. Once the onset, the condition of MSA progresses continuously, then leads to death or disabled, and the mean survival time is about 7-9 years. Based on the pathogenesis and pathological features, we reviewed the treatment and research highlights of MSA as follows.

Diagnostic criteria

The previous diagnostic criteria was according to symptoms and signs. The clinical symptoms include the different combination about striatum nigra degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome. It can be derived into MSA-P type which is manifested with Parkinsonian symptoms and dopamine poor outcome, and MSA-C type which has main manifestations of cerebellar ataxia. Both of two

types can combine with autonomic nervous dysfunction [4]. The 2008 second consensus statement established by Gilman etc defined MSA as sporadic, progressive and adult-onset (>30 year old) neurodegenerative disease, and included imaging characteristics such as atrophy of putamen, middle cerebellar peduncle, pons and cerebellum in MRI and hypometabolism of putamen, brain stem and cerebellum in FDG-PET.

Pathology features and pathogenesis

In 1989, Papp et al [5] found inclusion bodies in Oligodendrocyte are typical pathological changes in MSA patients. In 1998, Wakabayashi et al [6] found α -synuclein is the main ingredient of inclusion bodies in Oligodendrocyte. And inclusion bodies with α -synuclein inside were also found in the neurons of Parkinson disease, Alzheimer's disease, and Huntington dementia patients, which indicates that there is a same pathogenesis in these diseases and MSA, and they are called α -synuclein disease. The α -synuclein is in inferior olivary nucleus, pontine nucleus, cerebellum, substantia nigra,

locus coeruleus, putamen, pallidum, subthalamic nucleus and intermediolateral column of thoracic spinal cord, lower motor neuron and cortical cone neurons [7], and the distribution density is positively correlated with degree of neuropathy. According to the studies, researchers found the possible pathogenesis of MSA is because of abnormally gathering of hyperphosphorylation of α -synuclein which leading to degeneration of Oligodendrocyte, and inducing degeneration and loss of myelin, activating microglia, causing oxidative stress and inflammatory reaction, and leading to degeneration and death of neurons [8-10]. Besides, immunoinflammatory response is also found in the pathogenesis of MSA [11, 12]. Additionally, the intravenous injection of immunoglobulin can relieve the symptoms of MSA patients in clinical study [13], which indicates that the immune-mediated mechanism may also involve in the pathogenesis of MSA.

Treatment in current situation

Now there is no effective medicine to cure MSA, most part of methods are symptomatic treatment and enhanced care. The main research direction of treatment includes immunization transplantation and cytotherapy.

1. Parkinsonism: Levodopa, monoamine oxidase inhibitor, or combination of them, but has no apparent results [14].
2. Orthostatic hypotension: Midodrine Hydrochloride or Pyridostigmine Bromide can reduce the difference of blood pressure between erect position and supine position [15].
3. Urinary and bowel disorders: Antidiuretic hormone analogues or Trosipium Chloride is for urinary incontinence, but with caution because of its central nervous system side effect. Catheterization is for much residual urine, and Laxative is for astriction [16].
4. Cerebellum ataxia: Cholinergic agents are advised for a try by some studies, which could increase cholinergic transmitter in the brain [17] and improve the symptoms, but there is no any effect to confirm it.
5. Change the life style and increase the rehabilitation and exercises: Stretch socks, avoiding hot environment, changing the position slowly, balance exercises and other rehabilitation methods.

In recent years, many kinds of stem cells have been found by researchers and they are trying to treat MSA and other degenerative diseases which hope to relieve the degeneration of neurons.

Stem cells

Stem cell as “universal cell” has significant superiority in treatment of neurodegenerative diseases because of its particular biological characteristic. In recent years, researches about stem cells increase quickly both in basic and clinical trials. In 2010, FDA approved the global first case of Oligodendrocyte precursor cell in human embryonic stem cells for treatment of acute spinal cord injury in human testing. Soon afterwards, stem cell was approved in clinical trials in many countries such as England, Swiss, Korea and China, and in last year, umbilical cord blood cell was also approved in enlarging clinical treatment by FDA. In China, since 2016, 114 stem cell clinical research record organizations were supported of clinical application transformation by Chinese National Health and Family Planning Commission and the Food and Drug Administration.

Stem cells are derided into embryo stem cells and adult stem cells according to their sources. The later one includes neural stem cells, mesenchymal stem cells, induced pluripotent stem cells [18] and umbilical cord blood mononuclear cells. Otherwise, embryo stem cells were restricted in basic researches because of its ethical issues and induced teratomas [19]. Adult stem cells are approved to use in both preclinical and clinical trials.

Neural stem cells

Neural stem cells exist in cerebral ventricles, hippocampus and striatum of brain tissues, and they have self-renewing ability and differentiation potentiality [20]. In vitro and in vivo trials it has shown that they can differentiate into neurons and gliocytes. The researchers found that in mice models of neurodegenerative diseases, the stem cells can migrate into the lesions of the brain (cortex, hippocampus and striatum) to proliferate and differentiate into three kinds of nerve cells including neurons [21, 22]. Neural stem cells are ideal donors for MSA by replacement treatment. Nonetheless, it is difficult to obtain the neural

stem cells because they are in the central nerve system. Moreover, it is restricted by ethics problems if taking them from the brain of the aborted fetus and using the embryonic stem cells.

Mesenchymal stem cells (MSCs)

MSCs mainly include bone marrow MSCs, umbilical cord MSCs, adipose tissue-derived MSCs and gingiva-derived MSCs [23-31]. The MSCs are widely used because they are easy to obtain, and they have powerful self-renewing and differentiation ability, quick ex-vivo expansion, easy mediated gene transfer and other advantages, and they have very little possibility of oncogenicity [32-34]. In a mice trial, the bone marrow MSCs were transplanted into the MSA-P type mice, the Parkinsonism symptoms got improved because of the neuroprotective and immune-regulation effects [35]. Some similar animal experiments have verified that MSCs could decrease cytokines of TNF- α and IL-1 releasing, inhibit immuno-inflammatory reactions, and reduce the activation of astrocytes and gliocytes in the brain of MSA animal mode. It has been confirmed that the proliferation of astrocytes and gliocytes is negatively correlated with survival levels of the neurons [36, 37].

In a recent study, the MSCs were injected into the internal carotid artery of MSA animal mode to observe the security and effectivity, and the results were that there was no ischemic changes in brain MRI, and in the treatment group, the survival amount of neurons in striatum and substantia nigra increased significantly and dyskinesia symptoms relieved obviously, which indicates that this method could be safe and effective [38]. Lee [39] found that after 1 year follow-up, in the treatment group of 33 MSA patients, the UMSARS and cognitive ability are better than the control group, and the glucose metabolism rate and grey matter concentration in cerebellum and cerebral cortex were higher than in the control group. He also found there was no any serious side effects correlating with MSCs during treatment and follow-up period.

The basic research found that MSCs also have secretion ability [40]. Some proteomic analysis was made about the substances secreted by MSCs. The researchers found that there were many important neuromodulators including cystatin C, glia-derived nexin, galectin-1, vaso-

lar endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), IL-6, Glial cell line-derived neurotrophic factor (GDNF) and so on. These secretion substances were injected into substantia nigra and striatum of the animal mode, the dopaminergic neurons increased and the motor behavior got improved in the animal mode [41]. It indicates that MSCs not only can differentiate into and replace the damaged nerve cells, but have secretion and secretagogue function. We speculate MSCs secrete neuroprotective substances which can change the microenvironment of the lesions of MSA patients, regulate immunity, inhibit inflammatory reaction, protect nerve cells, and promote the endogenous neural stem cells to gain the differentiation and secretion functions, which contributes to treat and improve the symptoms of MSA.

Human umbilical cord blood-mononuclear cell (hUCB-MNC)

Human umbilical cord blood is the residue of blood in the placenta and umbilical cord after fetal delivery. It is the most abundant cell bank and its usage is not limited to treat hematological diseases. In October 2017, a comprehensive clinical research of umbilical cord blood cells was developed at Duke University School of Medicine, which included patients with autism, cerebral palsy, hydrocephalus, language disorders and cerebral ischemia. They found the most important cells in the umbilical cord blood are mononuclear cells which had nerve regeneration function [42]. Besides of the proliferation and differentiation functions, hUCB-MNC also has many advantages such as simple and convenient collection and separation, noninvasive, no ethics controversy, low antigenicity and longer survival time [43, 44]. The researches about hUCB-MNC treatment on α -synucleinopathies diseases such as Parkinson disease, dementia and MSA, or on neuron motor disease increased gradually.

HUCB-MNC is a mixed cell group. Besides some kinds of stem cells and ancestral cells such as hematopoietic stem cells, MSCs and endothelial progenitor cells, it also includes regulatory T cells, natural killer cells, T lymphocytes and dendritic cells, and these cells have protective functions in generating and developing process of neurodegenerative diseases [45]. Human umbilical cord blood cells have high level of

CD34+ and CD105+ cytological markers, which means they have high regenerative potentiality [46]. This was also found in many *in vitro* studies, and it even has higher directional differentiation functions. It can differentiate into nerve cells and replace the degenerative ones in special environment [47-49]. In animal experiments, after hUCB-MNC was transplanted into the brain, it could not only secrete nerve growth factors [50-52], but promote endogenous neurotrophic factors to release [53], to protect neurons and repair the damaged cells, and rebuild the regeneration microenvironment. Professor Gong [54, 55] and her colleagues found the clinical scores of MSA improved significantly, their daily life skills enhanced obviously. The conditions of 3 cases got significantly improvement in 3 days, and it was impossible for the stem cells to differentiate into nerve cells, so it was probably because hUCB-MNC changed the pathogenic micro-environment. Other studies also indicated that hUCB-MNC has positive effect in nerve system diseases treatment by regulating immunity [56-58]. In recent years, some researches showed that inflammatory and immune mechanisms were involved in the pathogenesis of MSA. So hUCB-MNC may play roles by many aspects including differentiation, replacement, secretion, changing micro-environment, inhibiting inflammation and regulating immunity and so on.

It is important to choose the appropriate way of stem cell transplantation treatment for MSA. The effective treatment not only depends on the characteristics of the donor cells, but relies on if the stem cells can migrate to central nerve system and integrate into the lesion tissues. Some researchers found stem cells which were transplanted by intravenous injection partly passed through blood-brain barrier, and the ones transplanted by carotid artery led to minor cerebral embolism [59]. The lateral ventricle puncture would damage the brain and may have complications such as intracerebral infection and cerebrospinal fluid fistula. The stereotactic technique usually used in the neurosurgery operation is chosen for limited lesions, but it is difficult to use in MSA patients because of the wide lesions. Lateral atlanto-occipital space puncture is an ingenious way created by Professor Dianrong Gong [60] and it can be used as a replacement and supplementary method of lumbar puncture. This method has been used safely and reliably in clinic for more

than 20 years. In 2011, Professor Gong transplanted stem cells into the brain by lateral atlanto-occipital space puncture. The needle is inserted through lateral atlanto-occipital space behind the ear, and hUCB-MNC is injected into cisterna magna. More than 200 kinds of refractory nerve system diseases have been treated by this method, which included more than 30 cases of MSA with fine clinical effect and without serious complications. It indicates that stem cells treatment may be valid for refractory nerve system diseases.

Conclusions

MSA is a neurodegenerative disease with extensive lesions, gradual progress and poor prognosis. Some common methods used in clinic could only improve few symptoms of patients but it could not cure it radically and improve the outcomes. Stem cell has many characteristics such as self-replication, self-renewal, differentiation and secreting neurotrophic factors, and it can serve as a more effective intervention method for MSA and other refractory neurological diseases. Though the basic experiments and clinical researches of stem cell are increasing gradually, we should concern about its safety and validity, if it can survive after transplantation into human body, how it can integrate well with host, how it can play therapeutic effect. Furthermore, there is no standardization about choice of stem cell types, stem cell amounts, choice of treatment method and so on. In spite of many difficulties of treatment of neurodegenerative diseases such as MSA, stem cell treatment would be a prospective method in the future.

Disclosure of conflict of interest

None.

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