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Journal of Stem Cell Research and Therapy

Case Report

Can Umblical Cord-Derived Mesenchymal Stem Cells be used in Retinal Diseases: A Case Presentation of Leber Congenital Amaurosis

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ABSTRACT

Human umblical cord blood is an excellent source of stem and progenitor cells which increase secretion of neurotrophic factors. These cells are known to have neuroprotective effect in neurodegenerative processes. The numbers of clinical reports including implantation of stem cells in retinal diseases are increasing rapidly. This paper aimed to review the safety and efficacy of umblical cord derived mesenschymal stem cell implantation in retinal pathologies. We also present the first clinical case of a hereditary retinal disease called Lebers' congenital amaurosis with the sixth month follow-up results after stem cell treatment.

Keywords: Leber congenital amaurosis; Retinal diseases; Suprachoroidal implantation; Umblical cord-derived mesenchymal stem cell

INTRODUCTION

Degenerative retinal diseases cause progressive irreversible vision loss in early stages of life. Usage of stem cells in the treatment of these retinal diseases is a fairly new and popular topic in ophthalmology. Many researchers consider that the transplantation of Mesenchymal Stem Cells (MSCs) is the most effective way of cell therapy. Simultaneous activation of multiple mechanisms (paracrine, trophic, immunomodulatory, and differentiation) affects all stages of the regeneration of damaged tissues. It has been reported that umblical cord derived MSCs (UCMSCs) increase secretion of neurotrophic factors, angiogenic chemokines and angiogenic growth factors [1,2]. There are experimental studies demonstrating successful results of UCMSCs applications in degenerative retinal diseases [3,4] and to date there is no data about this type of stem cell implantation in human.

Leber congenital amaurosis (LCA) is an inherited retinal disorder characterized by severe visual impairment from birth or within the first months of life. It is the most common cause of congenital blindness which is also known as early onset form of retinitis pigmentosa (RP). The disease is thought to be caused by abnormal development of photoreceptor cells, or by the premature degeneration of retinal cells. After successful outcomes of phase III studies, the first gene therapy drug named voretigene neparvovec (LuxturnaTM) is approved by FDA for the treatment of LCA and other retinal dystrophies. Luxturna is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation. It is recommended for the patients who have viable retinal cells in early stages of the disease [5].

This clinical case aimed to investigate the safety and efficacy of suprachoroidal UCMSC implantation in a patient with LCA. To the best of our knowledge, this is the first case report including the results of UCMSC treatment in LCA.

CASE PRESENTATION

In this report, we describe a 36-year-old female patient with the clinical diagnosis of LCA who received suprachoroidal UCMSC implantation. The patient had low visual acuity since childhood and her visual acuity decreased to light perception in her both eyes at the age of 7 years. Her vision was only light perception in both eyes at presentation. She had nystagmus and poor pupillary light responses. Fundus examination showed bilateral pale optic disc and severe peripheral pigmentary retinopathy. The electroretinography (ERG) testing was undetectable in both eyes and she was unable to do the visual field testing due to the low vision. Optic cohorence tomography (OCT) testing showed atrophic retina and choroid in both eyes. Foveal thickness was

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Received Date: October 01, 2021; **Accepted Date:** October 13, 2021; **published Date:** October 19, 2021.

Citation: Oner A, Kahraman NS (2021) Can Umblical Cord-Derived Mesenchymal Stem Cells be used in Retinal Diseases: A Case Presentation of Leber Congenital Amaurosis. J Stem Cell Res Ther. 11:002.

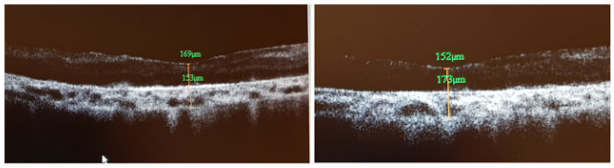
169 microns and choroidal thickness was 153 microns in the right eye. Her systemic examination was normal.

The patient was informed about gene therapy and genetic testing for RPE65 (this gene is the only treatable one) was performed. Unfortunately the RPE65 gene of the patient was found to be normal and there was no chance for gene therapy under current conditions [5]. Therefore we gave information about stem cell treatment option and written informed consent about stem cell therapy was obtained from the patient and her parents. After the approval by the Review Board of Stem Cell Applications of the Ministry of Health according to the regulations in our country (Review number for approval: 56733164/203), the patient received suprachoroidal UCMSC treatment to the right eye.

The details of the stem cell preparation were as follows: Umbilical Cord was disinfected and cut into pieces of 1-2 mm^2. The pieces transferred to 75-cm^2 culture flasks in DMEM-LG containing 10% HS (Human Serum), and 1% penicilin +streptomycin and cultured at 37°C in 5% CO^2. Culture medium was changed with fresh medium once every 3 days and waited for 70% confluency. Culture-expanded cells at the third passage were examined for surface protein expression by using flow cytometry. The UCMSCs were positive for CD 73, 90, 105 and negative for CD 34, 45, HLA-DR. No evidence of bacterial or fungal contamination was observed in the cells which were tested before releasing. Cell viability evaluated by trypan blue exclusion was >90.0%±0.5 before cell transplantation. 2 x 106 cells/ml in isotonic solution containing 1% human serum albumin were transferred in vials with the temperature controlled bag in 12 hours. The product was used in 24 hours [3].

The surgery was carried out under local anesthesia. We performed a surgical technique defined as Limoli Retinal Restoration Technique (LRRT) which was described by Limoli et al [6] and was also applied in another study of our group and found to be safe. [7] The details of the surgery are as follows: The globe was deviated to the supero-nasal quadrant and conjunctiva was dissected at the infero-temporal quadrant at 8 mm from the limbus. A deep scleral flap of about 5 X 5 mm was opened by radial hinge at the infero-temporal quadrant. The sclerectomy was deep enough to allow viewing of the color of the choroid. A flap from the orbital fat was extracted from a gap above the inferior oblique muscle. This tissue was laid on the scleral bed and sutured with 6/0 vicryl at the proximal edge. The scleral flap was then sutured above the fat pedicle. The remaining space between the autologous fat graft, choroid, and scleral flaps was filled with 1 cc of 2 x 106 UCMSCs. The conjunctiva was sutured with 8/0 vicryl [6,7].

On the examination at 6 months after treatment best corrected visual acuity improved to hand motion at 1 meter in the treated eye. There was also an improvement in the self-reported visual acuity and the patient mentioned that she was able to distinguish some colors after the treatment. We found no difference in the examination of visual field and ERG testing. There was a reduction of the nystagmus frequency compared to baseline and to the fellow eye. Furthermore, we found an improvement in the pupillary constriction of the treated eye compared to the untreated eye. We also found a thickening of the choroid (increased from 153 microns to 173 microns) which may demonstrate the improvement in the choroidal blood flow after stem cell treatment (Figure 1). There were no systemic or ocular adverse events related to the surgical procedure of the patient.



1A 1B

Figure 1A and 1B: OCT frames showed poor image quality due to the nystagmus of the patient. Note the disintegration of the retinal layers, the thinning of the retina and the choroid in both images. The choroidal thickness increased from 153 microns (1A) to 173 microns (1B) after treatment.

DISCUSSION

In recent years, there have been significant developments about stem cells therapies for retinal diseases. Clinical studies showed that implantation of stem cells for advanced retinitis pigmentosa is safe and had no serious advers effects [8-10]. In the Reticell-clinical trial, the investigators analyzed the effect of intravitreal use of autologous bone marrow derived MSCs (BMMSCs) to the quality of life of 20 patients with RP [8]. They found a statistically significant improvement in the quality of life of patients 3 months after treatment, whereas by month 12 there was no statistically significant difference from baseline.

In the largest ophthalmology stem cell clinical trial, seventeen patients with bilateral visual loss due to RP were included and followed up at least 6 months. Affected eyes were treated with 'The Stem Cell Ophthalmology Treatment Study' (SCOTS) protocol. In 33 treated eyes, 15 eyes improved an average of 7.9 lines of Snellen acuity, 15 eyes remained stable, and 3 eyes worsened by an average of 1.7 lines of Snellen acuity [9].

Another recent study [10] included 11 patients with end-stage RP who received subretinal implantation of adipose tissue derived MSCs and only one patient experienced an improvement in visual acuity (from 20/2000 to 20/200), visual field, and ERG. Three patients mentioned that the light and some colors were brighter than before and there was a slight improvement in visual acuity. The remaining seven patients in the study had no vision improvement (five of them only had light perception before surgery).

Human umbilical cord blood is widely used as a rich and ethically acceptable source of stem cell and is known to have higher proliferative potential than the other sources of MSCs like bone marrow and adipose tissue. In all clinical studies UCMSCs administration had no side-effects [2].

Treated 36 eyes of 25 dry age related macular degeneration patients with surgically grafted autologous cells and adipose tissue derived MSCs to the suprachoroidal space with his LRRT surgical technique. After 6 months the treatment improved

visual performance in 19 eyes (52.78%) and no adverse effects were reported in any case in this study Limoli et al [6].

In the current case report, LRRT was used as a stem cell implantation technique in our patient without any ocular complications and we found improvement in visual performance of the treated eye at 6 month follow-up. Up to date no standardized treatment modality has been proved including the route of delivery for the stem cells. Suprachoroidal technique was applied in another study of our group in retinal diseases and it was found to be safe with no systemic or ocular complications and effective for stem cell implantation [7].

CONCLUSION

In conclusion, stem cell based treatment modalities have been showing promising results in commonly encountered retinal diseases that currently have no curative treatment options. We believe that UCMSCs can be an effective stem cell source in the near future and stem cell therapies will hold an important place in the treatment of degenerative retinal diseases.

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