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Research Article

Suprachoroidal Umbilical Cord-Derived Mesenchymal Stem Cell Transplantation for the Regeneration of Glaucomatous Optic Neuropathy: A Preliminary Investigation

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Abstract

Objective: This preliminary research presents clinical findings from patients with advanced Glaucomatous Optic Neuropathy (GON) who underwent transplantation of Umbilical Cord-Derived Mesenchymal Stem Cells (UCMSCs) into the suprachoroidal space.

Methods: This prospective, single-center study included 17 eyes of 17 patients diagnosed with GON, who received suprachoroidal UCMSC implantation. Patients were registered if their visual acuity and/or Visual Field (VF) deteriorated despite maintaining good intraocular pressure control with anti-glaucomatous treatments. Evaluations were conducted at baseline, on the first postoperative day and at 1 month, 6 months and 1 year after surgery. Best Corrected Visual Acuity (BCVA), anterior segment and fundus examination, color photography, Optical Coherence Tomography (OCT), Retinal Nerve Fiber Layer (RNFL) analysis, VF testing and Pattern Visual Evoked Potential (PVEP) assessments were performed at baseline and during follow-up visits.

Results: All 17 participants completed the 12-month follow-up period. No systemic or serious ocular complications were recorded. The study showed significant improvements in BCVA, VF results, RNFL measurements and PVEP amplitudes at the end of the follow-up period.

Conclusion: Although the sample size is limited, suprachoroidal UCMSC therapy appears to be safe, with encouraging improvements. Further studies with larger patient groups and longer follow-up periods are required to assess the impact of stem cell delivery on visual acuity and quality of life in glaucoma patients.

Keywords: Glaucomatous Optic Neuropathy; Retinal Nerve Fiber Layer; Optical Coherence Tomography

Introduction

Glaucoma is a condition that damages the optic nerve of the eye, resulting in vision loss and if left untreated, it can cause complete blindness. It is the leading cause of irreversible blindness globally, affecting over 70 million individuals. The disease leads to dysfunction, gradual decline and degeneration of Retinal Ganglion Cells (RGCs). Elevated Intraocular Pressure (IOP) is the main factor contributing to RGC deterioration in glaucoma. Damage to RGCs results in vision impairment and blindness, as they are the neurons responsible for transmitting visual information from the retina to the brain [1,2].

Currently, the available treatment for glaucoma involves reduction of IOP which prevents the loss of RGCs. The pharmaceutical and surgical treatment available today targets trabecular meshwork, which is responsible for the drainage of the aqueous humor. Early intervention is crucial for slowing the progression of the disease and preserving the vision [1-3].

Significant efforts have been made to develop neuroprotective therapies aimed at preventing optic nerve damage. Unfortunately, there is no definitive evidence that these anti-glaucoma agents can halt the disease's progression entirely. The ineffectiveness of the current treatment in regeneration of optic nerve has led to the exploration of stem cells as a possible treatment option for glaucoma. Mesenchymal stem cells (MSCs) are being extensively studied for their neuroprotective properties in degenerative optic nerve disorders. The umbilical cord is commonly used as a rich and ethically favorable source of MSCs, offering several benefits, such as higher proliferative capacity and better quality compared to other stem cell sources. Besides these cells can be harvested without any invasive procedures to the patients. MSCs have demonstrated anti-apoptotic, anti-inflammatory, immunomodulatory and angiogenic properties. They offer trophic support for the neuroprotection and regeneration of damaged RGCs, either through direct secretion of neurotrophic factors or via indirect paracrine support. MSCs also have the potential to form new functional neural synaptic connections [4-6].

There are numerous preclinical studies in the literature which show the beneficial effect of stem cell applications in glaucoma [7-10]. A recent clinical study reported an increase in visual performance of glaucoma patients after implantation of autologous MSCs in the suprachoroidal space [11]. In this study, we aim to assess the safety and effectiveness of suprachoroidal Umbilical Cord-Derived MSC (UC-MSC) transplantation in patients with Glaucomatous Optic Neuropathy (GON). To the best of our knowledge, this is the first clinical study in the literature utilizing UC-MSCs as a source to restore GON.

Methodology

Study Design and Setting

This study included 17 eyes from 17 glaucoma patients who were examined in the ophthalmology department of our hospital between 01.01.2019 and 01.06.2022. The study was conducted in alignment with the Declaration of Helsinki, with approval from the University's Ethics Committee (Number: 2017/480, Date: 13.10.2017) and the Stem Cell Applications Review Board of the Ministry of Health (Registration number: 56733164/203) following national regulations. All participants provided written informed consent before participation in the study.

Patients

Patients with at least one year of follow-up after being diagnosed with primary open-angle glaucoma were assessed for study eligibility. Patients who experienced a decline in visual acuity and/or Visual Field (VF) despite well-controlled Intraocular Pressure (IOP) during follow-up were considered eligible. Following a thorough medical history review and standard ophthalmological examination, the patients were evaluated based on the study's inclusion and exclusion criteria.

The inclusion criteria were:

- Age 40 or older
- Clinical diagnosis of glaucoma confirmed by tests, including perimetry and Optical Coherence Tomography (OCT)
- Glaucomatous optic neuropathy (GON) with a cup/disc ratio of at least 0.6
- Best corrected central visual acuity (BCVA) of 20/50 or worse
- Abnormal visual field
- Receiving medical or surgical treatment for glaucoma
- Visual field deterioration despite stable intraocular pressure (IOP ≤ 19 mmHg)

The exclusion criteria were:

- Previous eye surgery other than cataract or glaucoma surgery
- Presence of dense cataracts or other media opacities that would alter ocular imaging or VF assessment
- Coexisting ocular diseases (e.g., retinal disorders, uveitis, strabismus, nystagmus)
- Systemic or neurological conditions that could affect study outcomes
- Smoking habit (due to its toxic effect on stem cells)
- Use of medications toxic to the optic nerve
- Inability to provide written informed consent
- Inability to attend all follow-up visits

Ophthalmologic Examination

The diagnosis of GON was confirmed for each patient through clinical evaluation and ophthalmological tests. A baseline ophthalmic evaluation was performed for all participants, including BCVA, applanation tonometry, pachymetry, slit-lamp biomicroscopy, color fundus photography, OCT, Retinal Nerve Fiber Layer (RNFL) analysis and VF testing. Visual acuity was measured using a Snellen chart at a distance of 3 meters. OCT was performed using the Nidek RS-3000 Advance 2 (Japan). The VF examination utilized the 30-2 program of the Humphrey Field Analyzer (Carl Zeiss Meditec, AG, Germany). Pattern Visual Evoked Potential (PVEP) tests were conducted with Metrovision (France).

Stem Cell Preparation

The source of the stem cells was umbilical cord tissue, which was donated to the Laboratory for research purposes. The tissue was disinfected and cut into 1-2 mm^2 pieces, which were placed in 75 cm^2 culture flasks containing Dulbecco's Modified Eagle's Medium-Low Glucose (DMEM-LG) with 10% Human Serum (HS) and 1% Penicillin/Streptomycin. The cultures were maintained at 37°C with 5% CO_2 concentration and the medium was changed every 3 days until the cells reached 70% confluence. The culture-expanded cells at the third passage were analyzed for surface protein expression using flow cytometry.

The UC-MSCs were positive for CD-73, CD-90 and CD-105, but negative for CD-34, CD-45 and HLA-DR. No bacterial or fungal contamination was detected in the cells, which were tested before being released. Cell viability, assessed by the Trypan Blue dye exclusion test, was 90.0% ± 0.5 before transplantation. A concentration of $5x10^6$ cells in an isotonic solution with 1% human serum albumin was transferred to vials in temperature-controlled bags within 12 hours and the product was used within 24 hours.

Surgical Technique

An experienced surgeon (AO) performed all surgeries under local anesthesia. The surgical method used was the Limoli Retinal Restoration Technique (LRRT), as described by Limoli, et al., [12]. However, in this study, a different stem cell source and dose were used. Each eye received 5 million UC-MSCs. This technique was previously described in previous clinical studies.

Postoperative Follow-up

Patients were hospitalized for one day after surgery and topical antibiotic and steroid drops were applied four times daily for one month. Ophthalmic evaluations, including BCVA, anterior and posterior segment examinations, were performed before surgery and at 1 day, 1 month, 3 months, 6 months and 12 months post-surgery. Color fundus photos, OCT, RNFL analysis and VF tests were conducted before surgery and at 1, 3, 6 and 12 months postoperatively. PVEP tests were carried out at baseline and at the 12-month visit. All patients were monitored for any adverse effects of the surgery throughout the study period.

Statistical Analysis

Data were analyzed using the SPSS version 20 statistical software package. Descriptive statistics are presented as the arithmetic mean ± Standard Deviation (SD) and median (Min-Max) for non-normally distributed numerical variables, while frequencies and percentages are provided for categorical variables. The Shapiro-Wilk test was used to determine the distribution of numeric data. Categorical variables were analyzed using the Pearson Chi-square test. Quantitative data with normal distribution were tested with one-way ANOVA (post hoc Scheffé), while non-normally distributed data were analyzed using the Wilcoxon Signed Ranks test. A p-value of less than 0.05 was considered statistically significant.

Results

Seventeen eyes from 17 patients with GON completed the one-year follow-up period. The average age of the participants was 55.6 ± 18.2 years, ranging from 45 to 82 years. Thirteen were male and four were female. Nine patients had the treatment in the right eye, while eight received it in the left. The average age of disease onset was 45.6 ± 18.7 years and the mean duration of the disease was 13.1 ± 7.9 years. During at least one year of follow-up in our clinic before the stem cell surgery, all patients experienced deterioration in BCVA and/or VF. All patients were on topical anti-glaucoma medications; seven were using two types of eye drops and ten were using three. Five patients had previously undergone trabeculectomy surgery. The demographic details of the patients are listed in Table 1. Following suprachoroidal UC-MSC implantation, there were statistically significant improvements in BCVA and VF results at the end of the 12-month follow-up period ($p < 0.05$). The average BCVA at the beginning was 0.18 ± 0.15 (range 0.01-0.40) Snellen line, which improved to 0.33 ± 0.29 (range 0.01-0.70) Snellen line at the end of the first year. This change was statistically significant ($p < 0.05$).

Regarding VF test results, the mean deviation (MD) at baseline was -27.81 ± 8.36 (range -20.11 to -32.42). By the end of the first year, it improved to -25.19 ± 8.73 (range -16.02 to -34.41), a statistically significant improvement ($p < 0.05$).

For the mean RNFL thickness, measurements at baseline were 104.82 ± 30.20 μm and 114.02 ± 28.58 μm after 12 months, showing a significant difference ($p < 0.05$). The test results are presented in Table 2 and Fig. 1 shows the VF improvement of a patient. None of the patients showed any morphological abnormalities in OCT scans of both eyes after stem cell treatment. No severe systemic or ocular side effects were observed during the 12-month follow-up period. There were no complications related to the surgery, either during or after the procedure. There were some minor side effects, including conjunctival hyperemia, itching, pain with eye movements and abnormal color vision, all of which disappeared within the first month after surgery. The mean IOP values recorded before and after surgery did not show a significant change ($p < 0.05$). The average IOP at baseline was 13.76 ± 1.64 mmHg (range 10-17) and 13.33 ± 1.39 mmHg (range 10-15) at the end of the first year.

The average corneal thickness measured before surgery was 533.31 ± 46.34 μm and it was 529.47 ± 42.45 μm after surgery, which was not statistically significant ($p < 0.05$). By the end of the study, BCVA had improved in 14 eyes (82%), remained unchanged in 2 eyes (12%) and deteriorated in 1 eye (6%).

Regarding PVEP results, the latencies of the P100 wave did not change post-treatment, but the amplitudes of P100 significantly improved from 3.74 μV to 5.21 μV after stem cell implantation ($p < 0.05$) (Fig. 1). All patients successfully completed the 12-month follow-up period.

Characteristics (n=82)	
Age (years), mean ±SD	55.62 ±18.2 (45-82)
Sex (male), n (%)	13 (76.4)
Age at the diagnosis (years), mean±SD	45.6±18.7
Duration of the disease (years), mean±SD	13.1±7.9
Corneal thickness (μm), mean±SD	533,31±46,34
Operated eye side, n (%)	
OD	9 (53)
OS	8 (47)
OD: Oculus Dexter, OS: Oculus Sinister, SD: Standard Deviation	

Table 1: Demographic details of the patients.

Outcomes		**Preoperative**	**Postoperative 1 year**	***P* value***
BCVA (Snellen)	Mean±SD	0.18±0.15	0.33±0.29	<0.05
IOP (mmHgA)	Mean±SD	13.76± 1.64	13.33± 1.39	>0.05
VF (dB)	Mean±SD	- 27.81±8.36	-25.19±8.73	<0.05
RNFL Thickness (μm)	Mean±SD	104,82±30,20	124,02±28,58	<0.05
VEP amplitude (μV)	Mean±SD	3.74	5.21	<0.05
VEP latency (msn)	Mean±SD	99.58	97. 93	>0.05
BCVA: Best Corrected Visual Acuity, SD: Standard Deviation, IOP: Intraocular Pressure VF: Visual Field, dB: decibel RNFL: Retinal Nerve Fiber Layer, VEP: Visual Evoked Potentials, μV: mikrovolt, msn: Milisecond * Related-Samples Friedman's Two-Way Analysis of Variance by Ranks test was used.				

Table 2: Comparison of BCVA and VF findings (μm: Micrometer).

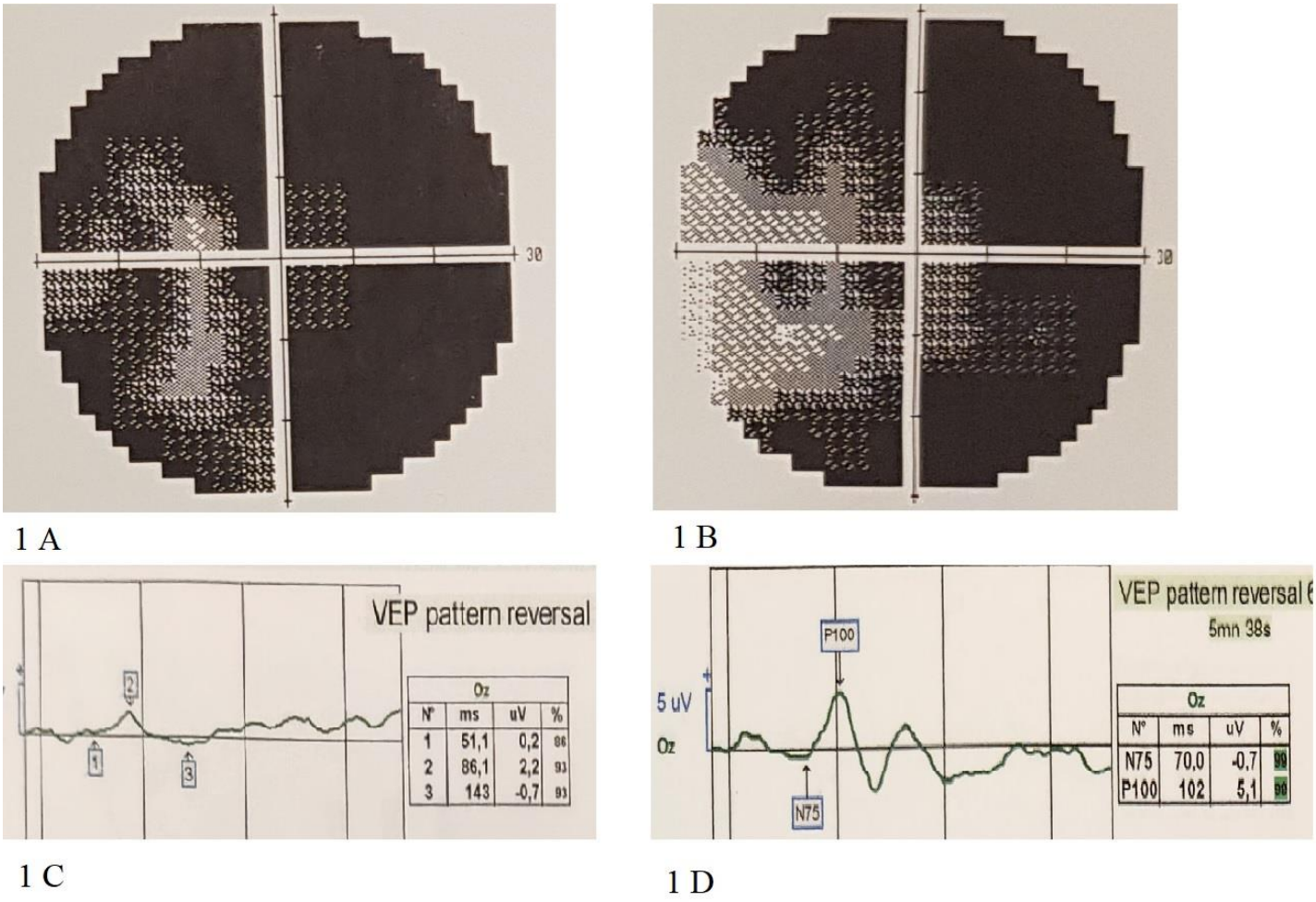

Figure 1: Perimetry results of a GON subject before treatment (1A) and one year after treatment (1B). Note the improvement in central visual field during the first year period. PVEP results of the same subject during the study period (1C and D). Note the improvement of the P100 amplitude.

Discussion

Intraocular Pressure (IOP) is a critical risk factor in the advancement of glaucoma. Currently, therapies aimed at reducing IOP are the only proven strategies to slow the progression of GON. IOP can be lowered through medications, laser treatments or surgical procedures. Although a variety of drugs and surgical techniques effectively reduce IOP, they are sometimes insufficient to stop glaucoma from worsening. As a result, many ophthalmology researchers have turned their attention to exploring the mechanisms behind neuronal survival and developing neuroprotective therapies to complement existing treatments [16].

Previous research has shown that MSC implantation in degenerative diseases can modulate the local environment through paracrine effects by releasing neurotrophic factors such as basic fibroblast growth factor, neural growth factor, ciliary neurotrophic factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. These factors promote the survival of retinal cells and activate internal repair mechanisms. MSCs also support neuronal growth, encourage synaptic connections, promote blood vessel formation, modulate inflammation and reduce demyelination and cell death, all contributing to their neuroprotective and regenerative properties [17].

Numerous animal models of glaucoma, which are dependent on IOP, have shown that MSC implantation can promote the survival of RGCs, prevent RGC loss and protect the trabecular meshwork tissue [8,18-20].

In a recent study by Emre, et al., the authors investigated the neuroprotective effects of both bone marrow derived and adipose tissue derived MSCs that were intravitreally transplanted in an experimental Ocular Hypertension (OHT) model. They reported

that the RGCs were significantly improved in stem cell-treated OHT groups compared with that in the non-treated OHT group. The results of immunohistochemical analyses showed integration of a limited number of stem cells into the ganglion cell layer and the inner nuclear layer. There was also a decrease in the number of cells expressing proinflammatory cytokines in the MSC-transferred OHT group compared to the non-treated OHT group. They concluded that, after intravitreal transplantation, MSCs showed a neuroprotective effect in the rat OHT model and this therapy can be an alternative for functional recovery in the treatment of glaucoma [8].

In another recent experimental study, researchers transplanted either intravitreal or systemic bone marrow-derived MSCs for neuroprotection in a rat model of laser-induced ocular hypertensive glaucoma. The study showed that intravitreal MSC administration led to a significant increase in RGC axon survival and a decrease in RGC axon loss. Systemic transplantation did not result in MSC migration to the eye and had no effect on optic nerve damage. The researchers recommended further investigation of autologous intravitreal MSC transplantation as a potential neuroprotective treatment for glaucoma [18].

Wang, et al., investigated the ability of transplanted hUC-MSCs to survive and migrate within the vitreous cavity and their neuroprotective effects on chronic glaucomatous retina. Intracameral transplanted hUC-MSCs migrated toward the area of damaged retina, but did not penetrate into the retina. The study showed that hUCMSCs were efficient at decreasing the loss of RGCs; retinal damage was reduced through the inhibition of apoptosis. In this study, the authors demonstrated the prolonged neuroprotective potential of intravitreal hUC-MSCs in chronic glaucoma [10].

There are a few clinical reports in the literature which include MSC transplantation in glaucoma patients. In a recent case report by Vivela, et al., the authors reported the results of a single intravitreal application of autologous bone marrow-derived MSCs in 2 eyes of 2 patients with open-angle glaucoma in advanced stage of optic neuropathy (ClinicalTrials.gov, NCT02330978, 01.05.2015). The patients had a cup/disk ratio worse than 0.9, visual field MD index lower than- 15 dB, visual acuity of light perception, but controlled IOP. Patients did not show improvement on visual acuity or VF after treatment. In addition, one patient developed retinal detachment with proliferative vitreoretinopathy. The authors concluded that, while animal models have demonstrated successful outcomes, caution is needed when translating stem cell therapy to clinical use in humans [21].

Various methods of MSC administration have been explored in several clinical studies for the management of degenerative optic nerve diseases. Extraocular approaches such as suprachoroidal, subtenon and retrobulbar injections have the advantage of delivering cells without surgical complications since these techniques do not involve the vitreous. Suprachoroidal method used in this study, was reported to have no serious complications and was considered to be safer when compared to the intravitreal or subretinal applications [11]. Our study also proved that suprachoroidal method could be applied without systemic and ocular complications.

There are a few clinical studies reporting on extraocular stem cell applications. The largest clinical trial, known as the Stem Cell Ophthalmology Treatment Study (SCOTS), used retrobulbar, subtenon, intravitreal and optic nerve injections for MSC transplantation. In two cases involving autoimmune optic neuritis and idiopathic bilateral optic neuritis, no significant complications were observed [22]. Another SCOTS study involving 10 patients with bilateral visual loss due to non-arteritic ischemic optic neuropathy reported that 80% of patients experienced improvements in visual acuity, while 20% showed no change [23]. Another recent clinical study involved 29 eyes from 23 patients with optic atrophy (including 6 eyes from 5 glaucoma patients). Following suprachoroidal UC-MSC transplantation, the authors reported statistically significant increases in BCVA and VF without major systemic or ocular complications. It was suggested that stem cell treatment via suprachoroidal transplantation seems to be a safe and effective alternative therapy for optic nerve diseases that currently lack curative treatments [6].

A recent clinical study performed at the Low Vision Center in Milani included 35 eyes of patients diagnosed with GON. Twenty one eyes in the control group received no treatment, 14 eyes in the study group received LRRT treatment. In this technique an autograft was implanted to the suprachoroidal area including adipose stromal cells, adipose-derived stem cells and platelets derived from the platelet-rich plasma. It was reported that sensitivity, residual close-up and BVCA improved in the eyes of the patients who received treatment. However the patients in the control group reported a decrease regarding to the parameters above. The study reported no systemic and ocular complications during the follow up period [11].

In this current clinical study, umbilical cord tissue is used as the source of stem cells, which differs from the technique used in LRRT. To our knowledge, this is the first clinical study to use UC-MSCs in GON as a treatment option. Previous studies comparing the secretomes of Wharton's jelly from umbilical cords and bone marrow (WJ-MSCs and BM-MSCs, respectively) found that WJ-MSCs expressed more genes related to angiogenesis and neurogenesis. The study also reported that WJ-MSCs performed better in neural differentiation and neural cell migration through paracrine mechanisms. WJ-MSCs were identified as a superior MSC source for enhancing neurorestoration and angiogenesis *in-vivo*. We believe that preclinical studies provide a foundation for the development of clinical cell-based therapies like the one used in this study [24].

There are some limitations to our study. It is a preliminary investigation with a small number of patients, all in the late stages of the disease. Larger clinical trials with more patients with various disease stages and longer follow-up periods, including comparisons with control groups, are necessary to fully assess the clinical efficacy of this treatment.

Conclusion

As a conclusion, therapy with stem cells is a promising approach for glaucoma patients since it may enhance the regeneration of RGCs.

Conflict of Interests

The authors declare no conflict of interest in this publication.

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