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RETINAL DISORDERS

Autologous neurosensory free-flap retinal transplantation for refractory chronic macular hole—outcomes evaluated by OCT, microperimetry, and multifocal electroretinography

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Abstract

Purpose To report the safety, anatomical and functional outcomes of autologous neurosensory retinal transplant in patients with a refractory large unclosed macular hole.

Patients and methods This is a prospective case series of four patients with large chronic macular hole that underwent vitrectomy and free-flap neurosensory retinal transplantation surgery with silicone oil tamponade. The hole was closed with an autologous retinal transplant of an approximate diameter of 1.5–1.8 mm, harvested outside the vascular arcades. Anatomical and functional outcomes were assessed using best-corrected visual acuity (BCVA-Snellen), optical coherence tomography (OCT), OCT angiography, microperimetry (MP), and multifocal electroretinography (mfERG).

Results There were 2 male and 2 female patients with median age of 73 (60–81) years. The median follow-up period was 17 (13–23) months. The median preoperative size of the macular hole was 1872.5 (868–2591) μm at the widest basal diameter and 828 (556–1099) μm at the minimum diameter. Surgery resulted in the anatomical closure of the macular hole in all cases. The OCT showed structural integration of the transplant and reappearance of the inner segment ellipsoid to different extents. The BCVA improved from preoperative 0.1 (6/60; + 1.0 logMAR), 0.1 (6/60; + 1.0 logMAR), 0.05 (6/120; + 1.3 logMAR), and 0.005 (6/1200; + 2.3 logMAR) to 0.2 (6/30; + 0.7 logMAR) postoperatively in cases 1, 2, and 4, and to 0.1 (6/60; + 1.0 logMAR) in case 3. MP showed retinal function in the region corresponding to the area of the transplant (circle of 1.8 mm in diameter) in all patients after the surgery (median sensitivity in that region was 4.0 dB, range 1.8–12.4 dB). Improvement was noted in the patient that had MP performed before the surgery (mean sensitivity improved from 0 to 1.8 dB). Detectable function was mostly located in the peripheral regions of the transplant. Multifocal ERG showed abnormal function of the central ring and normal function of the second ring in 3 of 4 cases. The OCT angiography showed normal perfusion, without signs of neovascularization. There were no intra- or postoperative complications.

Conclusion Autologous retinal transplantation surgery is a successful technique for closing of large refractory macular holes. The procedure is safe and provides good anatomical results. Visual acuity, microperimetry, and mfERG suggest some gradual functional integration of outer regions of the transplants, but no central functional restitution has been detected as yet.

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This study was performed at the Eye Hospital, University Medical Centre Ljubljana, Grablovičeva ulica 46, 1000 Ljubljana, Slovenia.

This article is part of a topical collection on Macular Hole.

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Key messages

What was known

- Autologous retinal transplantation is a new surgical approach in the treatment of large refractory macular holes.
- It is a technically demanding procedure with high anatomical success rate.
- A part of the tissue that originates from the retina outside the macula lutea is transplanted into the central part of the fovea.
- The transplanted tissue was found to survive and morphologically integrate in the defect.

What this paper adds

- All our patients showed morphological integration of the neurosensory free flap in the adjacent retinal structure with anatomical restoration of the retinal layers in the macular region.
- Better recovery of the ellipsoid zone was seen in OCT in cases with subretinally positioned graft.
- Functional integration, as shown by mfERG and microperimetry, suggest some gradual functional integration of outer regions of the transplants.
- No central functional restitution has been detected as per up to 23 months after surgery

Keywords Retinal free-flap transplantation · Refractory chronic macular hole · Ellipsoid zone restoration · Vitrectomy · Macular surgery · Multifocal ERG · Microperimetry

Introduction

Macular hole is a retinal dehiscence located in the center of the fovea, causing decreased visual acuity, metamorphopsia, and central scotoma [1]. Its reported prevalence is 0.2–3.3 per 1000 persons [2].

There are two types of macular hole: idiopathic macular hole and secondary macular hole [1]. Risk factors for development of the idiopathic macular hole are age, ocular inflammation, and myopia. Macular holes occur most in the 6th and 7th decades of life with higher incidence in females [3].

Modern vitrectomy with different techniques of internal limiting membrane (ILM) peeling provides 95–98% closure rate of idiopathic macular hole [4–7]. On the other hand, treatment of patients with chronic large macular hole, patients with macular hole related to high myopia, or after trauma, represent challenging cases and may require multiple surgeries in order to achieve closure [5]. In comparison to fresh idiopathic macular holes, which have a higher closure rate [8–10], the postoperative (type 1) closure rate for large chronic macular holes is 83.7% [11].

Surgical approaches for refractory macular holes after previous vitrectomy with ILM peel are limited. The reported surgical methods are repeated vitrectomy [12], laser photocoagulation combined with gas tamponade [13], a simple gas tamponade [14], an expanded ILM stripping [15], and autologous ILM flaps [16–18]. If extensive ILM peeling was previously performed, harvesting a new suitable ILM free flap could be difficult. In those cases, lens capsular flap transplantation may be a solution [19], but not in phakic eyes or pseudophakic eyes with previously performed posterior capsulorhexis. Autologous neurosensory retinal free-flap transplantation has been reported as an alternative surgical approach in cases of refractory macular holes that underwent multiple surgeries and had no useful remnant ILM [20].

This is a prospective case series of four patients who underwent autologous neurosensory transplantation surgery for refractory large chronic macular hole. The purpose of the study was to evaluate safety, anatomical and functional outcomes of autologous neurosensory retinal transplant in patients with refractory large unclosed macular holes, and to compare the differences in the surgery outcome regarding epiretinal versus subretinal positioning of the graft.

Patients and methods

In total, four patients were included. Three patients with chronic macular hole had previously multiple vitrectomies and ILM peeling with gas tamponade. One of the patients had retinal detachment related to a large macular hole. The median follow-up period was 17 months (range 13–23). The median patient age was 73 years (range 60–81) and the gender distribution was equal—two male and two female patients—and all four eyes operated were on the left. The median preoperative size of the macular hole was 1872.5 μm (range 868–2591 μm) at the widest basal diameter and 828 μm (range 556–1099 μm) at the minimum diameter. Median axial length of the eyes was 23.59 mm (range 22.57–25.73 mm) (Table 2) with mean spherical equivalent − 0.25 ± 2.68 D, median value 0.0 D (range: − 2.75/+ 3.75).

The study was conducted from January 2017 until July 2018 at the Eye Hospital, University Medical Centre Ljubljana, Slovenia. The study design adhered to the tenets of the Declaration of Helsinki; written informed consent from all patients was obtained before the surgical procedure. Surgeries were performed by a single surgeon (XL). The success of the surgery was evaluated based on the closure of the macular hole and the visual acuity improvement. Anatomical success was defined as complete closure of the macular hole, determined by both ophthalmoscopic and optical coherence tomography (OCT) examination (type 1 closure, only flat/closed) [21]. The graft with clearly visible layers on OCT during follow-up was rated as better.

All patients were tested for distance visual acuity and reading speed. Visual acuity was tested using a Snellen eye chart. The results obtained were converted to logarithm of the minimum angle of resolution (logMAR) units. Reading acuity was examined of the affected eye with Jaeger charts (J) at a distance of 30 ± 5 cm with an addition of three spherical diopters to the best correction for far distance. J 1 is the smallest and J 16 the largest type [22].

In all cases, OCT (Heidelberg Engineering Spectralis, Heidelberg, Germany), OCT/OCT angiography (DRI Triton, Topcon, Tokyo, Japan), static microperimetry (MP1, Nidek Technologies, Padua, Italy), and multifocal electroretinography (mfERG) (Roland Consult GmbH, Wiesbaden, Germany) were performed at the last checkup.

In each case, structural OCT, OCT angiography, and fluorescein angiography were performed postoperatively. Topcon DRI Swept source—OCT used for OCT angiography—is a device which has a 100 KHz A scan rate using a wavelength of 1050 nm. The scan protocol for the 6 × 6 mm scan pattern was composed of 320 × 320 scans.

Static MP was performed after pupil dilation with topical 1% tropicamide. The grid (Humphrey 10–2) tested 56 retinal locations in the central 20°, with 2° resolution at threshold sensitivities from 0 to 20 dB. Stimuli of the size of Goldmann III target appeared for 200 ms and changed intensity in 4–2 strategy. The mean sensitivity (MS) of the whole tested area was calculated using the MP1 software. Additionally, the approximate area of the transplant (a circle with 1.8 mm (6.3°) diameter, centered at the fovea) was superimposed on the microperimetry and the MS within this area was calculated. In a similar fashion, the MS corresponding to the areas of the first and second mfERG rings were also determined. The preferred retinal locus for fixation (PRL) and fixation stability was recorded during the exam. The fixation stability was determined as the percentage of fixation points that centered inside the 2° or 4° area. These areas were determined by the MP1 software and were centered at the highest density of fixation points. Each patient underwent 2–6 MP exams in the period of 1–32 months after the surgery. One patient (P3) had also performed MP on the day before the surgery.

Multifocal electroretinography (mfERG) testing was performed according to ISCEV standards [23] with RETI scan system, version 3.20.15. The recording was performed with the HK-loop electrode [24], placed in the fornix of the lower eyelid, while the silver-chloride reference electrode was placed on the ipsilateral temple, and the ground electrode was positioned on the forehead. The pupils were dilated with 1% tropicamide (Mydriacyl®, Alcon, Belgium) and the examination was performed in each eye separately, while the other eye was occluded. Refractive errors were corrected with + 3.50 diopters due to dilated pupils. The distance of the stimulus was 260 mm. The stimulus was provided by cathode-ray tube monitor, the diameter of the stimulus was 60°, and the patient was instructed to fixate into the center of fixation cross that was extending to all four corners of the screen to facilitate central fixation (the diameter of fixation cross—60°). The stability of fixation was monitored by the camera, placed in front of the patient. The subjects were coached for steady fixation and in case of inappropriate fixation, the recording trial was repeated (if a patient could not preform appropriate fixation, the result was interpreted as unreliable, as in the case 3). The stimulus included an array of 61 hexagons, the luminance of white hexagons was 112 cd/m^2, and the luminance of dark hexagons was 1–2 cd/m^2 (96–98% contrast). The hexagons were modulated between light (L) and dark (D) according to a binary m-sequence (511 samples of the sequence: LDDDD, frame length: 16.67 ms, total length: 47 ms). The recording session consisted of eight trials with a duration of 47 s. The signals were band-pass-filtered between 5 and 100 Hz; smooth filter at 50 Hz was also used. The average concentric ring response

Table 1 Surgery characteristics and results at the last checkup

	Case 1	Case 2	Case 3	Case 4
Neurosensory retinal graft positioning	Subretinal	Subretinal	Epiretinal	Epiretinal
Location of the transplant regarding the macular hole	Edge to edge	Edge to edge	Overlap on one edge	Overlap on both edges
Closure of macular hole	Complete	Complete	Complete	Complete
Follow-up duration	23 months	19 months	13 months	15 months

Table 2 Patient characteristics: all patients were pseudophakic; in three cases, there was posterior capsulorhexis performed. One case had macular hole–induced retinal detachment. Two patients were emmetropic, one hypermetropic, and one myopic. Cases 1, 2, and 3 were re-operated several times with multiple ILM peelings and ILM free flaps. All patients had statistically significant visual acuity improvement

Patient	Case 1	Case 2	Case 3	Case 4
Age (year)	68	78	81	60
Gender	M	F	F	M
Preoperative OCT hole size—widest basal diameter (μm)	2334	1411	2591	868
Preoperative OCT hole size—minimal diameter (μm)	925	731	1099	556
Axial length (mm)	23.81	23.37	22.57	25.73
Co-existing ocular comorbidities	/	/	/	Retinal detachment
Preoperative VA: Snellen logMAR	0.1 (6/60) + 1.0 logMAR	0.1 (6/60) + 1.0 logMAR	0.05 (6/120) + 1.3 logMAR	0.005 (6/1200) + 2.3 logMAR
Distance VA at last follow-up: Snellen logMAR	+ 0.50–1.25/100 = 0.2 (6/30) + 0.7 logMAR	+ 0.75–1.0/50 = 0.2 (6/30) + 0.7 logMAR	+ 5.0 dsph = 0.1; (6/60) + 1.0 logMAR	− 0.25–1.25/35 = 0.2 (6/30) + 0.7 logMAR
Mean spherical equivalent	− 0.25	+ 0.25	+ 2.75	− 3.75
Silicon oil removal (months after surgery)	3	8	/	5
Postoperative reading speed (words per minute)	20	26	20	19

densities (nV/deg^2), provided by the Roland, were taken into the analysis. For evaluation of the function at the region of retinal transplant, the observation of response densities in first two rings was of higher importance. The first ring corresponded to the foveal 5° area (0°–2.5° viewing angle) and the second ring corresponded with parafoveal region up to 16° (2.5°–8° viewing angle). As 1° of visual angle is equal to 288 μm on the retina, without correction for shrinkage [25], the first ring tested the function approximately to 720 μm eccentricity (diameter 1440 μm) and the second ring from 720 to 2304 μm (diameter 4608 μm).

Surgical technique In all four cases, 23-gauge pars plana vitrectomy was performed. A full thickness autologous neurosensory retinal graft was taken from the superior part of the retina in all cases (Table 1, Online Resource 1). The size of the transplant ranged from 1.5 to 1.8 diameters of the macular hole size. The area was first marked with thermo-cauterization and the retinal graft was excised with scissors. The location around the harvest site was surrounded with laser spots. Location of the transplant was subretinal with edge-to-edge position in two cases. Two cases had epiretinal-localized transplant with an overlap over the temporal side in one case and both sides in the other case (Table 1). In all four cases, maximal care was taken to maintain intact the native retinal pigment epithelium in the area under macular hole. Internal tamponade with silicon oil (2000 cs) was performed in all cases.

Results

In all four cases, anatomical recovery with complete closure of macular hole was achieved. There were no intra- or postoperative complications. All patients had a transient increase of the intraocular pressure, which responded well to local anti-hypertensive therapy.

Modest visual acuity improvement of at least one line in Snellen charts (− 0.3 up to − 1.6 logMAR) was noted in all cases between preoperative and last checkup visit (Table 2). One patient was able to read Jaeger 9 with regular presbyopic correction; with magnifying glasses from the distance of 5 cm, three out of four patients could read Jaeger 3 and one patient, Jaeger 4. Average reading speed was 23.7 words per minute (Table 2).

OCT

The OCT analysis showed complete structural integration of the retinal transplant into the adjacent retina in cases 1 and 2 (Fig. 1). All retinal layers could be recognized in these two cases with clear ellipsoid zone. In the case 3, the transplant was integrated into the retina but not all layers could be recognized. In the case 4 with preoperative retinal detachment, there was a mild intraretinal edema after the silicon oil removal. The transplant remained in

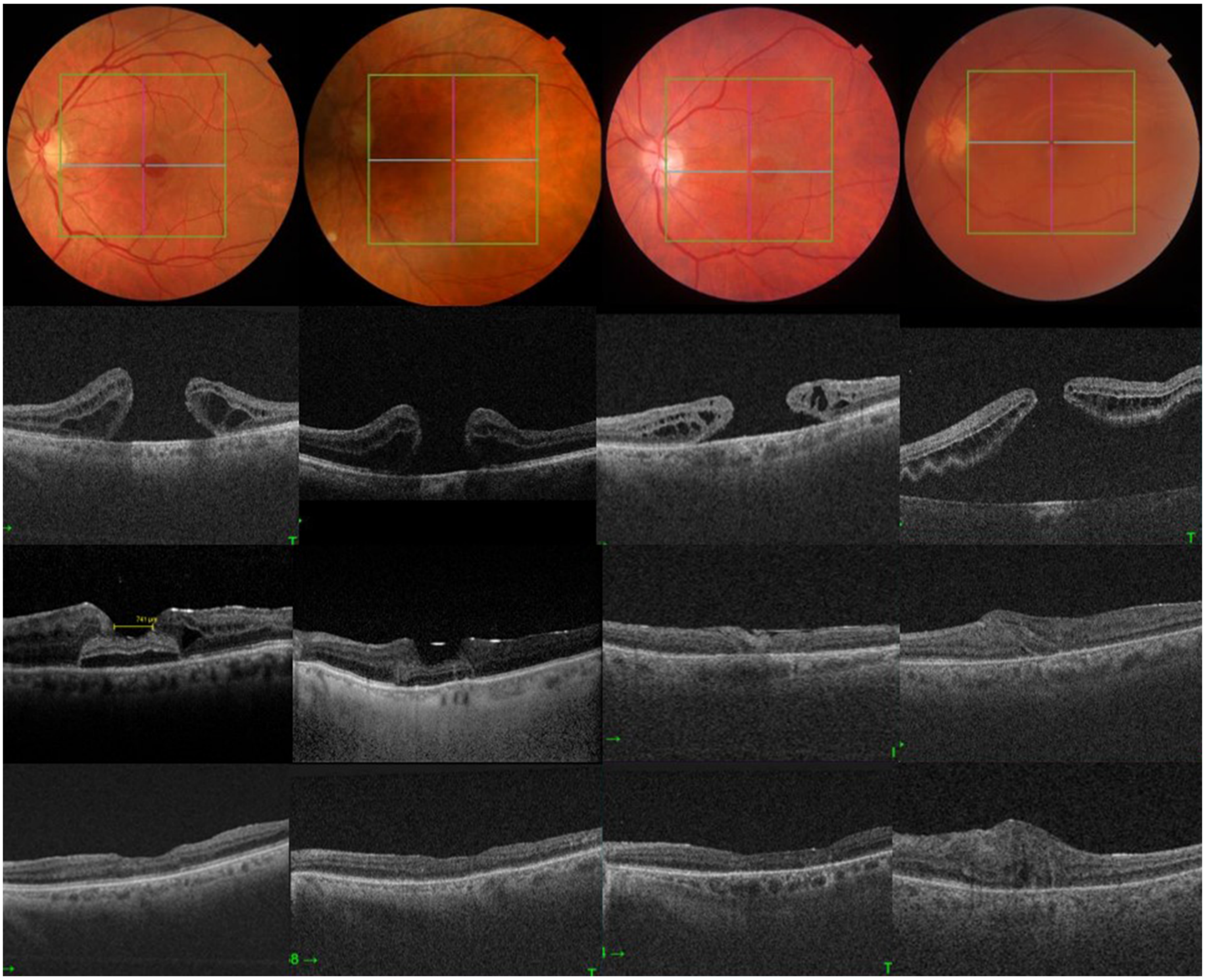


Fig. 1 Photo of the fundus and OCT findings. First row: preoperative photo fundus of 4 patients (P1, P2, P3, and P4) with chronic macular hole. Case 4 with macular hole–induced retinal detachment. Second row: preoperative OCT showing large chronic macular hole. Third row: first postoperative OCT; postoperative positioning of the graft under retina in P1 and P2; epiretinal positioned graft with the overlap on both edges in P3 and on one edge in P4. Fourth row: last checkup OCT with restoration of the ellipsoid zone in cases 1, 2, and 3 and mild intraretinal edema in case 4

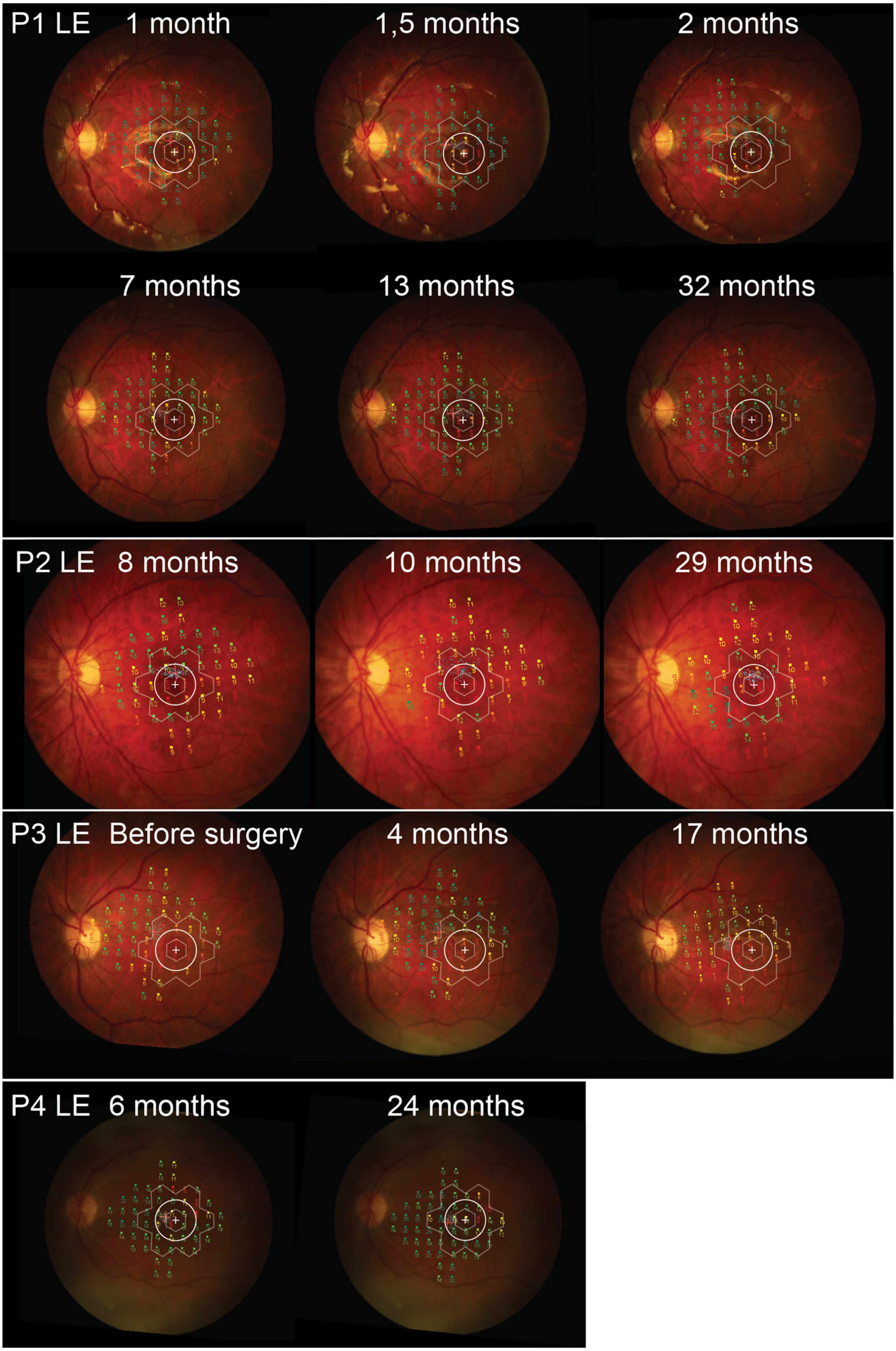
place with completely closed macular hole and retina attached (Fig. 1). The best anatomical results were obtained when the transplant was bigger and laid under the edges of retina. OCT angiography showed good perfusion without any signs of neovascularization (Online Resource 2).

Microperimetry

The main results of microperimetry examinations are presented in Figs. 2, 3 and Table 3. Additional data are presented in Online Resources 3, 4, 5. At the last follow-up microperimetry, the MS in the area of the transplant was 5.6 dB ± 4.8 dB; range, 2.5–12.4 dB. Spatially, the functional regions were located in the peripheral regions of the transplants while no function was detected in the region corresponding to the foveal center (Fig. 2). In patient 3, who had MP performed before and after the surgery, the MS improved from 0 to 1.8 dB. MP of the right eye with untreated macular hole of patient 3 are presented in the Online Resource 3. Mean sensitivity in the areas corresponding to the mfERG rings is presented in Online Resource 4. Fixation was relatively unstable and eccentric in all patients, located either in the nasal or nasal-superior perifoveal region, on or near the border of the transplant (Fig. 2, Online Resource 5).

Multifocal electroretinography

Multifocal ERG was performed in all patients after surgery (Fig. 4). In patient 3, due to a high degree of tremor, the quality of the recording was insufficient for further


P1 LE
1 month
1,5 months
2 months
7 months
13 months
32 months
P2 LE
8 months
10 months
29 months
P3 LE
Before surgery
4 months
17 months
P4 LE
6 months
24 months

◀ **Fig. 2** Microperimetry. The white circles delineate the approximate area where the retinal transplant was placed (1.8 mm diameter). Red cross marks the patients' fixation at the beginning of the exam; blue dots represent all fixation points during the exam. The areas corresponding to the 1st and 2nd mfERG rings are also projected on to the MP results. Note some retinal functions in the areas corresponding to the peripheral regions of the transplants and improvement of sensitivity in P3 who had MP performed before and after the surgery

interpretation. In patients 1, 2, and 4, electrophysiological presentations were similar. The responses from the retina stimulated by the 1st ring that also covered the region of the retinal transplant were reduced to approximately 50% of normative values. Responses from paracentral retina, covered by the 2nd ring, were of normal amplitudes (1st mfERG ring: 45.1, 42.1, and 56.4 nV vs. mean normal value: 91.6 nV, 2nd mfERG ring: 51.9, 45.1, and 48.0 nV vs. normal value: 40.8 nV).

Discussion

Management of refractory large macular hole represents a surgical challenge. This case series showed complete closure of the hole in all four patients. Autologous neurosensory retinal free flap was proposed as an option for the closure of the refractory myopic macular hole [26, 27]. Grewal and Mahmoud were the first who use an autologous neurosensory retinal free flap for the closure of refractory macular hole [27]. They used large free retinal graft and overlaid the hole with it. Wu et al. [28] also reported macular hole closure in four out of six patients by autologous retinal graft and blood clot. Ding and colleagues [29] reported complete closure in five patients with chronic large macular holes. Alternatively, Rizzo et al. [30] showed good anatomical and functional results in closing large chronic macular holes and retinal detachments with posterior macular holes by using amniotic graft. Some other studies report smaller closure rate of retinal graft transplantation for refractory macular holes in comparison to ILM free-flap transplantation [16–18]. Vitrectomy with a free-flap transplantation of autologous neurosensory retina can be applied also for patients who have undergone extensive ILM peeling and may not have a suitable ILM for transplantation.

Three out of four patients had prior vitrectomies with ILM peeling which failed to close the hole, while this procedure was successful in all cases. The fourth one had a macular hole–induced retinal detachment. Autologous retinal graft was placed under the edges of the hole in two cases, and over the edges of the hole in the other two cases, all showed complete closure of the hole regardless of the graft placement. The main advantage of the transplanted retinal graft is the fact that this technique provides complete full thickness autologous retinal graft which helps the macular hole to close. In comparison to the ILM free flap, neurosensory retinal graft is thicker, it does not easily drift away, subretinal fluid is absorbed by the retinal pigment epithelium, and the retina remains attached ensuring the glial proliferation, thus promoting the integration of the macular hole. This is of particular importance for macular hole-associated retinal detachments.

The recovery of the ellipsoid zone and the external limiting membrane have been reported as contributors to visual acuity improvement in macular hole cases after surgery [31]. OCT of our patients showed almost complete recovery of the ellipsoid zone in two cases with subretinal positioned graft and the integration of the neurosensory free flap in the normal retinal structure in all patients. Better recovery of ellipsoid zone and external limiting membrane in two cases with the graft placed under the edges of the hole can be explained by maximized interaction of the graft with the underlaying RPE in contrast to the cases with epiretinally positioned graft. Better contact with the RPE appears to enable better photoreceptor survival and better tissue integration. OCT angiography showed no signs of neovascularization with retinal perfusion restored. In the case with macular hole–induced retinal detachment, the retina completely reattached.

Beside morphological aspects of structural integration of transplanted retina, we evaluated also the possible functional integration of retinal grafts. Microperimetry showed partially preserved function in the regions corresponding to the peripheral parts of the transplants in all patients. The

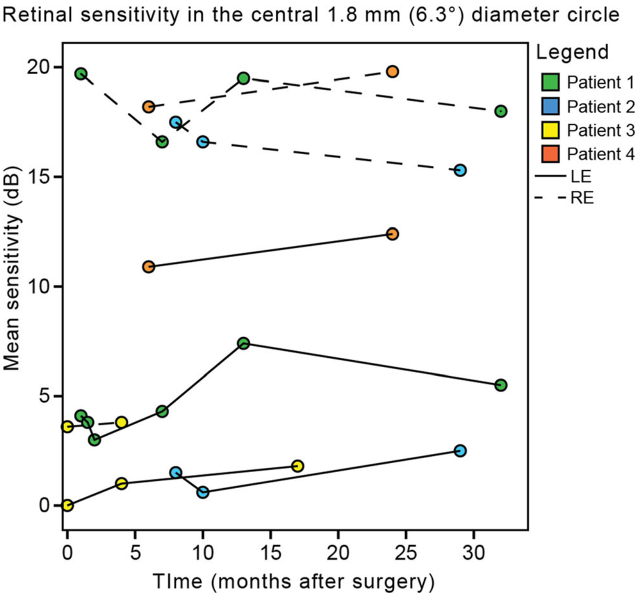


Fig. 3 Microperimetry in the area of the transplant. Mean retinal sensitivity measured by microperimetry in the area approximately corresponding to the location of the transplant (see Fig. 2) at different times after the surgery; and before the surgery for patient 3. Left (treated) eyes are marked with full lines and the right eyes with dashed lines (including an eye with an untreated macular hole in patient 3). There was a trend of increasing retinal sensitivity in the treated eyes in the months following the surgery. Note a similar fluctuation of sensitivity in the treated and untreated eyes, suggesting other modifying factors than the effect of the transplant

Table 3 Microperimetry results

ID	Time (months after surgery)	Silicone oil in the treated eye	MS of all tested locations LE	MS of all tested locations RE	MS in the central 1.8 mm (6.3°) ring LE	MS in the central 1.8 mm (6.3°) ring RE
1	1	Yes	16.6	19.6	4.1	19.7
1	1.5	Yes	16.9	N/A	3.8	N/A
1	2	Yes	15.8	N/A	3	N/A
1	7	No	12.7	16.5	4.3	16.6
1	13	No	15.5	18.5	7.4	19.5
1	32	No	14.9	18.1	5.5	18
2	8	No	10.4	18.2	1.5	17.5
2	10	No	7.1	16.1	0.6	16.6
2	29	No	8.2	16	2.5	15.3
3	0	Yes	9.8	9.8	0	3.6
3	4	Yes	13	13.6	1	3.8
3	17	Yes	8.2	N/A	1.8	N/A
4	6	No	14.3	18.2	10.9	18.2
4	24	No	16	19.3	12.4	19.8

RE = right eye, *LE* = left eye, *MS* = mean sensitivity, *NA* = not available

A circle with a diameter of 1.8 mm (6.3°) corresponding to the approximate area of the transplant

highest mean sensitivity in the transplant area was measured in patient 4 (12.4 dB) in which it was notably higher than in other three patients whose MS ranged from 1.8 to 5.5 dB. This could be related to the fact that patient 4 had the smallest diameter of the macular hole (556–868 μm) and consequentially a larger region of the remaining retina anatomically located in the measured area (1800 μm). Longitudinal improvement was observed in the case 3 with preoperative data. Since only this patient had MP before surgery, the pre-/postoperative analysis was limited. The MP also has relatively large test-retest variability: 2–3 dB for mean sensitivity and up to 5 dB for point-wise sensitivity [32–34]. According to the latter, the improvement observed in patient 3 (+ 1.8 dB in the area of the transplant) is below the limit of the test-retest variability. Fixation was relatively unstable and eccentric, with PRL located either in the nasal or nasal-superior perifoveal region. There was some variability in the retinal sensitivity on the operated eyes during follow-up; therefore, no conclusion can be made about shifting of PRL towards the graft and longer follow-up is needed to assess its functional capacity. Nevertheless, PRL localization will be a useful tool in further follow-up as it is for adjustment of optical aids for reading, as also shown in patients with Stargardt macular dystrophy [35].

For objective assessment of the macular function, mfERG was also used in 3 patients. All three had a reduced response with abnormal waveform morphology in the region of retinal graft. However, according to mfERG data only, it is not clear whether the measurable response originates from the graft region directly or from its surroundings. Having in mind that microperimetry showed no function in the central part of the transplant, central mfERG response might represent either the response of surrounding regions or the function of conserved photoreceptors and bipolar cells in the transplant region. Nevertheless, considering the restitution of the ellipsoid zone on the OCT, restitution of some function in the transplant area seems likely. It is not clear whether the transplanted cells are capable of establishing further neuronal connections. Rizzo et al. [30] in their study of macular hole closure with amniotic graft reported retinal ingrowth at the edges of the macular hole over the amniotic patch placed under the retina. This might explain microperimetry findings and better anatomical results in patients where retinal transplant was placed under the retina. Tabandeh [36] also reported revascularization of the retinal transplant in two cases with giant macular hole after autologous retinal transplantation, based on the OCT angiography findings. They concluded that the large avascular area of the transplanted tissue was the stimulation for angiogenesis. Based on our data (complete reperfusion of the graft in all four cases), revascularization was associated with structural integration of the avascular transplant regardless of its size, being 1.5–1.8 mm on average.

We are aware of the limitations of this small case series. One of the limitations of the study is that MP and mfERG investigations were only done postoperatively. However, comprehensive structural and functional assessment over a

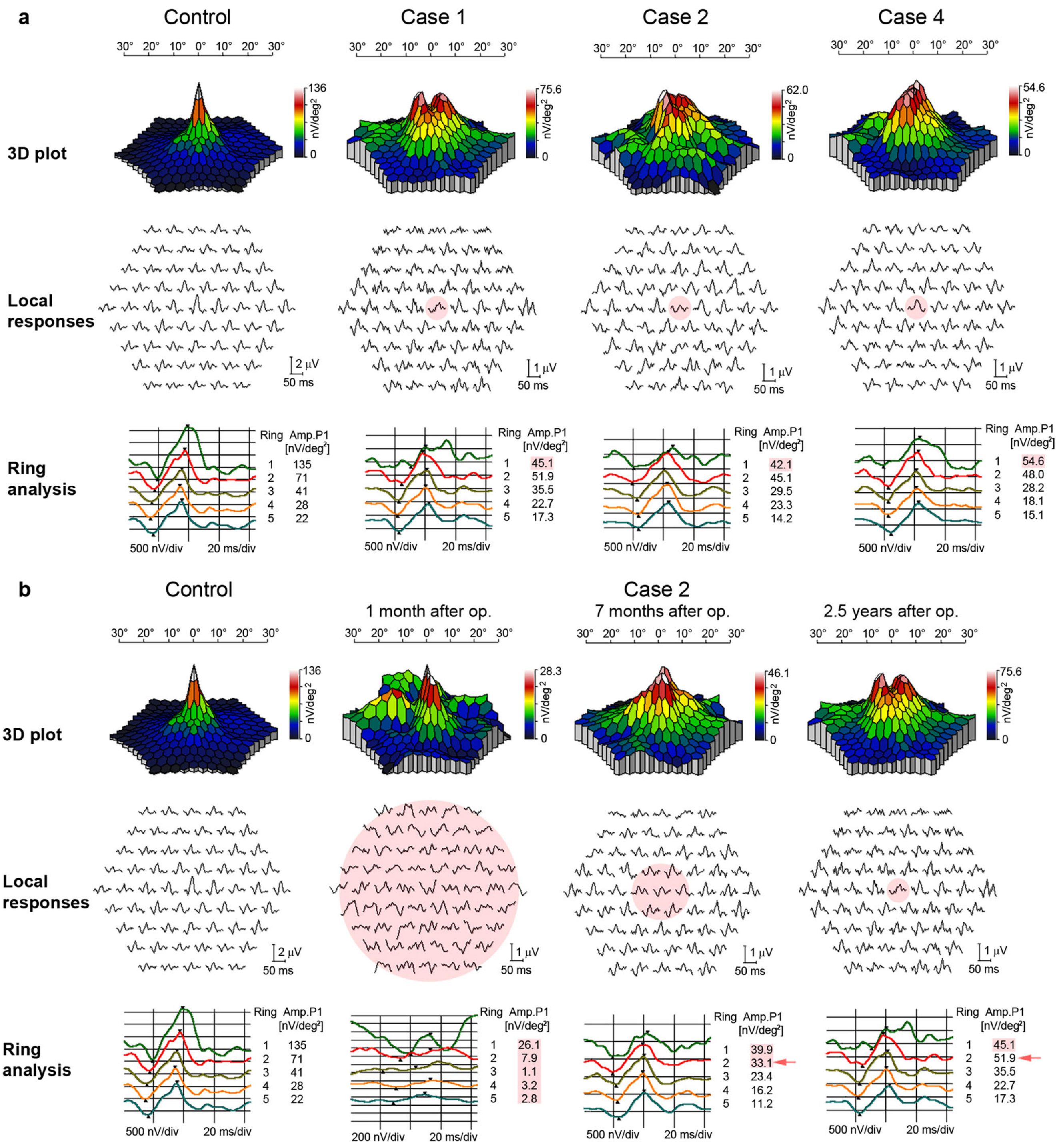


Fig. 4 Multifocal ERG results. **a** Multifocal ERG responses at the last checkup. Cases 1, 2, and 4 showed abnormal function in the central 5° region (marked with red area on the presentation of local responses and ring analysis). Responses in other regions of paracentral retina were normal. Multifocal ERG of the case 3 is not presented, as it could not be interpreted due to insufficient quality (muscular artifacts due to blinking and tremor). **b** Multifocal ERG responses on 3 consecutive visits of the case 1. One month after operation, the responses were reduced throughout the whole macular region (presumably due to the presence of silicone oil tamponade). The following visit 7 months after operation showed normalization of the retinal responses from the peripheral regions of central retina, while responses from the 1st and 2nd ring (corresponding with 0–2.5° foveolar and 2.5–8° parafoveolar region) were reduced. At the last checkup 2.5 years after operation, also the responses from parafoveolar regions normalized (marked with red arrow at the ring analysis)

relatively long follow-up period, which showed stable anatomical status of the fovea with follow-up longer than 12 months associated with gradual improvement of function, has not been published before. Despite excellent anatomical results, we must keep in mind the fact that even if some functional restoration would eventually ensue, the structure of the graft is not the same as the highly specialized normal fovea with spatial resolving capacity. The normal foveola has sophisticated cellular structure with absent inner nuclear and ganglion cell layer and densely packed cones, while transplanted peripheral neurosensory retina has a different structure mostly consisting of rods, which are not specialized for central vision. The question remains whether and to what extent the transplanted photoreceptors have the capacity to integrate and gain new functions in a new environment. Therefore, the possible potential of the transplanted patch for the creation of functional neural connectivity with the adjacent retina remains to be elucidated after longer follow-up.

Conclusion

Vitrectomy with the transplantation of autologous neurosensory retinal free flap can be an effective addition to the surgical options for large chronic MHs with or without retinal detachment even after failed surgery with ILM removal or transplantation. All grafts showed long-term viability, reperfusion, and structural integration regardless of whether the edges were placed epiretinally or subretinally although best anatomical results were obtained when the transplant was laid under the edges of surrounding retina. OCT revealed clear anatomical improvement with reappearance of ellipsoid zone associated with modest improvement of visual function according to visual acuity testing, as well as possible improvement of the peripheral regions of the transplant using microperimetry.

Authors' contributions All authors contributed to the study conception and design. Surgeries were performed by Xhevat Lumi. Material preparation, data collection, and analysis were performed by Xhevat Lumi, Sanja Petrovic Pajic, Maja Sustar, Ana Fakin, and Marko Hawlina. The first draft of the manuscript was written by Sanja Petrovic Pajic and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

Data availability All the data are available upon request.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of all images in Figs. 1, 2, and 4, as well as images in Online Resources 1, 2, and 3.

Code availability Not applicable.

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