Original Article

Optical coherence tomography analysis of surgical outcomes of combined hamartoma of retina and retinal pigment epithelium

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Abstract:

PURPOSE: To evaluate the surgical outcomes in combined hamartoma of retina and retinal pigment epithelium (CHRRPE) using optical coherence tomography (OCT).

METHODS: This was a retrospective interventional study, in which medical records of 12 eyes with CHRRPE that underwent vitrectomy and membrane peeling at three tertiary vitreoretinal institutes were reviewed. Preoperative and postoperative color fundus photographs and OCT were reviewed for each follow-up visit.

RESULTS: Five out of 12 eyes had a good visual outcome (equal or more than 2 lines gain in visual acuity), four had stable visual outcome (<2 line gain), and three had poor visual outcome (loss of visual acuity). Preretinal fibrosis preoperatively was seen in 80% of cases with good outcomes as compared to 50% and 0% of cases in the cohorts with stable and poor outcomes, respectively. Preoperatively all 5 cases with good visual outcome had Grade 4 epiretinal membrane (ERM), while only 1 case with stable and poor visual outcome had grade 4 ERM and the rest had Grade 3 ERM. Maxi peaks were seen in 80%, 50%, and 0% of cases preoperatively in the three cohorts, respectively. Hyperreflectivity of inner retinal layers preoperatively was evident in all cases having good visual outcomes, in 75% of cases with stable visual outcomes, and in 33% of cases with poor outcomes.

CONCLUSION: Surgical intervention in CHRRPE with preretinal fibrosis seems to be beneficial. The visual recovery as defined by conventional predictors in cases of surgical removal of ERM fails to explain the visual outcome in CHRRPE.

Keywords:

Combined hamartoma of retina and retinal pigment epithelium, optical coherence tomography, surgical outcomes

Introduction

Combined hamartoma of retina and retinal pigment epithelium (CHRRPE) has been described as a congenital benign entity[1] presenting with retinal disorganization, pigment migration, and gliosis accounting for vitreoretinal interface changes such as vascular tortuosity, preretinal fibrosis, epiretinal membrane (ERM) formation, and inner retinal layer distortion.[2] Vision loss in cases of CHRRPE[3] could be attributed to amblyopia, macular location, inherent retinal dysplasia, and secondary vitreoretinal interface changes. Retinal distortion, distortion of foveal contour and macular edema, as a consequence of contraction of ERM and preretinal fibrosis, seems to be the only factor amenable to surgical correction (vitrectomy and membrane peeling) in CHRRPE. However, there have been controversial reports in the literature citing evidence both in favor[4-6] and against[7,8] the surgical intervention in such cases due to variable prognosis. The natural course and progression of secondary vireoretinal interface changes in CHRRPE remains to be explored, creating a void in the definite management protocol, both in terms of appropriate timing and indications for intervention in such cases.

Hereby, in an optical coherence tomography (OCT)-based retrospective analysis, we report the visual and anatomical outcomes and the

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possible predictive factors in eyes with CHRRPE, which underwent vitrectomy and membrane peeling.

Methods

This was a multicenter collaborative retrospective analysis of medical records and retinal imaging from 12 eyes of 12 patients diagnosed with CHRRPE who underwent surgical intervention at three tertiary vitreoretinal institutes from Italy and India from January 2011 to April 2018. The local institutional review boards approved the study and the procedures adhered to the tenets of the Declaration of Helsinki.

Patient eligibility

Patients with a clinical diagnosis of CHRRPE who underwent imaging with color fundus photography or multicolor images "[Zeiss FF 450 (Carl Zeiss Meditec AG, Jena, Germany), DRI OCT Triton (Topcon, Medical Systems, Inc. Tokyo, Japan), TRC-50 IX camera (Topcon, Tokyo, Japan), Optos® (Optos PLC, Dunfermline, Scotland, United Kingdom)] and OCT imaging with either swept-source OCT (DRI OCT Triton; Topcon, Medical Systems, Inc. Tokyo, Japan), spectral-domain (SD) OCT (Heidelberg Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), and Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, CA) were included. The clinical diagnosis of CHRRPE was made on the basis of clinical characteristics as described by Gass.[1]

Criteria for surgery included progressive loss of vision, presence of prominent secondary vitreoretinal changes such as ERM and preretinal fibrosis, and subsequent macular distortion. Standard three-port, 25G pars plana core vitrectomy (Constellation Vision System, Alcon Laboratories Inc, Fort Worth, TX, USA), removal of posterior hyaloid and peeling of the glial component of the CHRRPE (internal limiting membrane forceps Grieshaber Revolution DSP 25G) were performed for each case by three experienced vitreoretinal surgeons. Only patients with a minimum follow-up duration of 3 months were included in the analysis.

Cases with any other coexisting retinal disease contributing to ERM, subretinal scarring, extensive fibrosis or prominent back shadowing on OCT obscuring the outer retinal details, and inconclusive diagnosis were excluded. Eyes with time-domain OCT or poor quality SD OCT scans were also excluded from the study.

Patient evaluation

The data collection included information on patient demographics, ophthalmic features, clinical features, and imaging findings of CHRRPE. Patient demographics included age and sex of the patients. Ophthalmic findings included preoperative and postoperative best-corrected visual acuity (BCVA) in Snellen fraction converted into logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Good visual outcome was defined as 2-line gain in visual acuity at the last documented follow-up visit, while gain in visual acuity <2 lines was considered as stable visual outcome. Any loss in visual acuity was considered as poor visual outcome. Slit-lamp evaluation included anterior segment workup findings and intraocular pressure measurement by applanation tonometry (mmHg).

Clinical evaluation

Based on color fundus photography, only macular variants of CHRRPE, who underwent surgical intervention, were selected for analysis.

Optical coherence tomography analysis

All patients underwent imaging on SS-OCT or enhanced depth imaging SD-OCT preoperatively and postoperatively at every visit. Raster scans centered over each CHRRPE were analyzed. The quantitative evaluation of OCT images included central macular thickness (CMT) measurements at baseline and at last follow-up using the built-in caliper tool. Qualitative variables that were assessed on OCT included:

A. Grades of ERM (1/2/3/4),[9] preoperatively
B. Presence or absence of preretinal fibrosis,[1] preoperatively
C. Presence or absence of infolding of inner retinal layers (Maxi peaks),[10] preoperatively
D. Presence or absence of inner retinal layer hyperreflectivity, preoperatively
E. Marked or minimal restoration of outer plexiform layer (OPL) contour (Saw tooth[10]/Omega sign[11]), postoperatively
F. Marked or minimal restoration of inner retinal layer infolding (Maxi peaks), postoperatively.

Statistical analysis

Data were analyzed using SPSS 20.0 software for Windows (SPSS Inc., Chicago, IL, USA), and linear regression analysis was performed to compute the correlation coefficient (r) and statistical significance (P value).

Results

Surgical outcomes of 12 eyes of 12 patients diagnosed with CHRRPE, who underwent standard three-port pars plana vitrectomy with membrane peeling, were evaluated. The mean age of the patients was 21.8 ± 13.3 years, and the cohort consisted of 8 males and 4 females. The mean BCVA preoperatively was 1.05 ± 0.46 logMAR (20/60–0.5/60) with a mean duration of vision loss of 8.3 ± 4.6 months. The mean postoperative BCVA was 0.89 ± 0.65 logMAR (20/25–0.5/60) after a mean follow-up of 6.75 ± 5.86 months.

For comparative statistical analysis [Table 1], subjects were divided into three cohorts based on visual acuity gain postoperatively: (1) eyes with good visual outcome (equal or more than 2 lines gain in visual acuity), (2) eyes with stable (<2 line gain in visual acuity), and (3) eyes with poor visual outcome (loss of visual acuity). Based on the postoperative visual acuity, 5 out of 12 eyes had a good visual outcome [Figure 1], 4 had stable visual outcome [Figure 2], and 3 eyes had poor visual outcome [Figure 3]. The mean age of the patients was 27.4 ± 19.2 years, 21.5 ± 5.4 years, and

Table 1: Comparative analysis of cases of combined hamartoma of retina and retinal pigment epithelium with good, stable, and poor visual outcomes after pars plana vitrectomy and membrane peeling

	Good visual outcome (>2 line gain in visual acuity) (*n*=5)	Stable visual outcome (<2 line gain in visual acuity) (*n*=4)	Poor visual outcome (decrease in vison) (*n*=3)
Age (years), mean	27.4±19.2	21.5±5.4	13±1.73
Preoperative mean BCVA (logMAR)	1.33±0.42	0.54±0.07	1.28±0.02
Postoperative mean BCVA (logMAR)	0.73±0.37	0.39±0.10	1.81±0.44
Mean follow-up (months)	4.8±5.76	5.0±5.41	12.3±4.04
Mean CMT (baseline) (μm)	699.6±135.3	605±110.9	508.3±3.78
Mean CMT (last follow-up visit) (μm)	445.6±37.38	421.5±126.5	437.3±43.0
Mean change in CMT (μm)	254±144.39	183.5±99.5	71.0±40.0
Grades of ERM	100% - grade 4	25% - grade 4	25% - grade 4
Preretinal fibrosis (%)	80	50	0
Inner retinal layer hypereflectivity (%)	100	75	33
Inner retinal folds (maxi peaks) (%)	80	50	0
Postoperative restoration of OPL (saw tooth/omega sign) (%)	60	25	0
Postoperative restoration of inner retinal folds (%)	100	25	0

BCVA=Best-corrected visual acuity; CMT=Central macular thickness; ERM=Epiretinal membrane; OPL=Outer plexiform layer; logMAR=Logarithm minimum angle of resolution

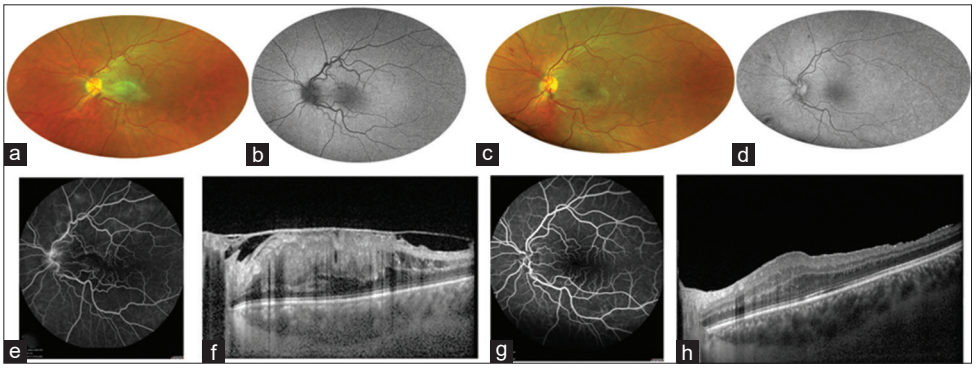

Figure 1: Good visual outcome. Multimodal image panel of a 19-year-old male patient with preoperative best-corrected visual acuity of 20/200 diagnosed with combined hamartoma of retina and retinal pigment epithelium. Preoperative multicolor image (a) shows predominant preretinal fibrosis surrounded by epiretinal membrane at the macula with corresponding hypoautofluorescence (b) along with vascular distortion, blocked fluorescence (corresponding to preretinal fibrosis), and diffuse patches of hyperfluorescence in late arteriovenous phase of fluoresceine angiography (e). Preoperative spectral-domain optical coherence tomography (f) shows a central macular thickness of 766μ along with Grade 4 epiretinal membrane and preretinal fibrosis, hyperreflective inner retinal layers, prominent inner retinal folds (maxi peaks), distorted outer plexiform layer configuration (omega sign), and preserved outer retinal layers. Eight months following pars plana vitrectomy and membrane peeling best-corrected visual acuity improved to 20/80 with multi color image (c) showing complete removal of epiretinal membrane and fibrosis with reduced hypoautofluorescence (d), vascular distortion, and fluorescein leak (g) as compared with preoperative images. Postoperative spectral-domain optical coherence tomography (h) shows reduction in central macular thickness to 415μ along with reduced vitreomacular distortion and marked restoration in configuration of inner retinal layers and outer plexiform layer

13 ± 1.73 years in eyes with good, stable, and poor visual outcomes, respectively. The mean BCVA improved to 0.73 ± 0.37 logMAR from 1.33 ± 0.42 (gain of 5.5 lines) over a mean follow-up period of 4.8 ± 5.76 months after surgical intervention in the subgroup with good visual outcome, while in the subset with stable visual outcome, the mean BCVA postsurgery had increased to 0.39 ± 0.10 logMAR from 0.54 ± 0.07 logMAR (gain of 2.5 lines) over a mean follow-up duration of 5 ± 5.41 months. The mean BCVA in the subgroup with poor visual outcome had decreased to 1.81 ± 0.44 logMAR from a baseline BCVA of 1.28 ± 0.02 (loss of 5 lines) over a mean follow-up period of 12.3 ± 4.04 months. The mean CMT at baseline was 699.6 ± 135.3 μm, 605 ± 110.9 μm, and 508.3 ± 3.78 μm, whereas at the last follow-up visit postsurgery, was 445.6 ± 37.38 μm, 421.5 ± 126.5 μm, and 437.3 ± 43.0 μm in the three cohorts, respectively.

Differences in the qualitative features on OCT were also assessed between the three cohorts. All of the 5 cases with good visual outcome had Grade 4 ERM preoperatively, while only 1 of the cases with stable and poor visual outcome had Grade 4 ERM and the rest had Grade 3 ERM. Preretinal fibrosis preoperatively was seen in 80% (4 out of 5) of cases with good outcomes as compared to 50% of cases (2 out of 4) and 0% of cases (0 out of 3) in the cohorts with stable and poor outcomes, respectively. Infolding of inner retinal layers (Maxi peaks) was seen in 80% (4 out of 5), 50% (2 out of 4), and 0% (0 out of 3) of cases preoperatively in cohorts with good, stable, and poor outcomes, respectively. Hyperreflectivity of inner retinal layers preoperatively was evident in all cases having good visual outcomes, in 75% of cases (3 out of 4) with stable visual outcomes, and in 33% of cases (1 out of 3) with poor outcomes.

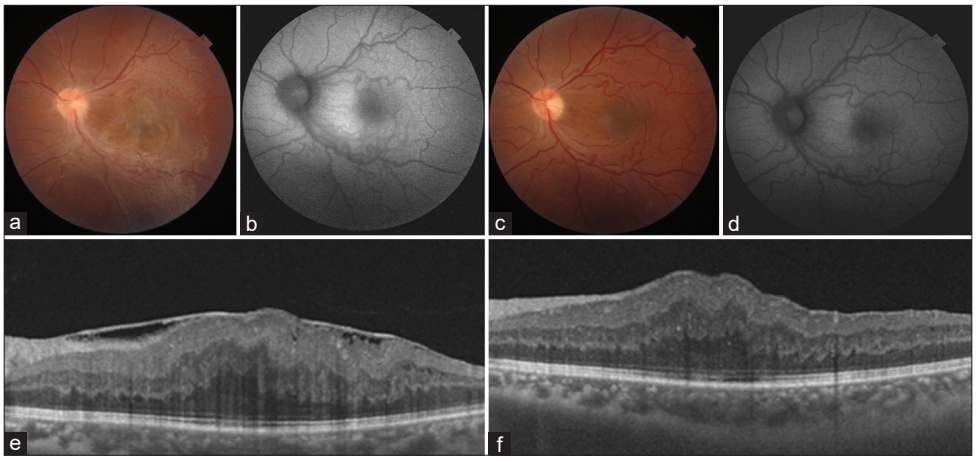

Figure 2: Stable visual outcome. Multimodal image panel of a 26-year-old male patient with preoperative best-corrected visual acuity of 20/60 diagnosed with combined hamartoma of retina and retinal pigment epithelium. Preoperative color image (a) shows prominent epiretinal membrane and vascular distortion at the macula with corresponding hypoautofluorescence (b). Preoperative spectral-domain optical coherence tomography (e) shows a central macular thickness of 620μ along with Grade 4 epiretinal membrane, minimal hyperreflectivity of inner retinal layers, prominent inner retinal folds (maxi peaks), distorted outer plexiform layer configuration (saw tooth appearance), and preserved outer retinal layers. Five months following pars plana vitrectomy and membrane peeling best-corrected visual acuity improved to 20/40 with color image (c) showing complete removal of epiretinal membrane with marginal change in autofluorescence (d) and vascular distortion as compared with preoperative images. Postoperative spectral-domain optical coherence tomography (f) shows reduction in central macular thickness to 550μ along with minimal restoration in configuration of inner retinal layers and outer plexiform layer

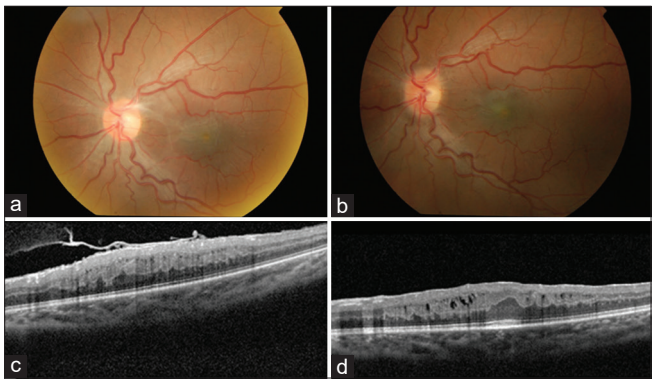

Figure 3: Poor visual outcome. Multimodal image panel of a 12-year-old male patient with preoperative best-corrected visual acuity of 3/60 diagnosed with combined hamartoma of retina and retinal pigment epithelium. Preoperative color image (a) shows prominent epiretinal membrane, subretinal greenish hue along with internal limiting membrane folds and vascular distortion at the macula. Preoperative spectral-domain optical coherence tomography (c) shows a central macular thickness of 511μ along with Grade 4 epiretinal membrane with a plane of cleavage seen temporal to disc, cystic spaces in inner retinal layer, minimal distortion of inner retinal layers, and distorted outer plexiform layer configuration (saw tooth appearance) along with preserved outer retinal layers. Ten months following pars plana vitrectomy and membrane peeling best-corrected visual acuity decreased to counting finger 1/2 meters with color image (b) showing complete removal of epiretinal membrane. Postoperative spectral-domain optical coherence tomography (d) shows reduction in central macular thickness to 438μ, persistence of cystoid changes along with minimal rest

In all the cases, complete surgical removal of ERM and preretinal fibrotic tissue was possible with reduction in vascular tortuosity postoperatively. Marked restoration of OPL contour (omega sign/saw tooth configuration) postoperatively (compared with baseline scans) was observed in 60% (3 out of 5) of cases with good outcomes and the rest 40% (2 out of 5) had minimal restoration in the contour of OPL postoperatively. Postoperative marked restoration of OPL contour was only observed in 1 case out of 4 with stable visual outcome subset. Similar trends were noticed for unfolding of inner retinal folds (maxi peaks) postoperatively, with all cases of good visual outcome and only 25% (1 case out 4) with stable visual outcome showing marked restoration of inner retinal layer configuration postoperatively. None of the cases in the cohort with poor visual outcome had restoration in the configuration of OPL or inner retinal layers postoperatively.

Statistical significance (p) was calculated using linear regression analysis for multiple variables in order to analyze the predictive value of each variable in relation to the visual outcome. However, due to the limitation of the sample size and follow-up duration, none of the values except for the grades of ERM were statistically significant (mean age: $P = 0.240$; preoperative mean BCVA : $P = 0.075$; mean CMT [baseline]: $P = 0.065$; mean change in CMT: $P = 0.115$; grades of ERM: $P = 0.009$; preretinal fibrosis: $P = 0.092$; inner retinal layer hyperreflectivity: $P = 0.108$; inner retinal folds [maxi peaks]: $P = 0.092$; and postoperative restoration of OPL [saw tooth/omega sign]: $P = 0.116$).

Discussion

Gass[1] in one of the earliest descriptions of CHRRPE proposed that the glial membrane causing vitreoretinal traction could be integral to dysplastic retina and attempts of removal can be hazardous to retinal architecture leading to suboptimal visual

outcomes postsurgery. However, histopathological examination of these membranes subsequently by Stallman[12] did not show any hallmark components suggestive of them being intrinsic to retina, and the composition was analogous to the structure of idiopathic ERM. Furthermore, in an SD-OCT-based description of CHRRPE, Shields *et al*.[10] concluded that ERM was distinct from underlying CHRRPE lesion.

CHRRPE although being a congenital entity, progressive visual loss has been described in 16%–24% of cases by Schachat *et al*.[13] The natural course of disease along with the sequence of development of secondary vitreoretinal changes remains to be determined, resulting in controversies in terms of visual outcomes after surgical intervention in CHRRPE. The report from the macular society group in 1984[13] showed improvement in only one out of three cases which underwent membrane peeling and vitrectomy. Similar results were shown by McDonald *et al*.,[7] where the authors demonstrated limited role of surgery in cases with long standing vision loss and macular edema. However, none of the studies evaluated preoperative OCT features in detail and their relationship with postopearative outcomes.

Good visual outcomes following vitrectomy and membrane peeling in CHRRPE have been reported by Sappenfield and Gitter,[8] Konstantinidis *et al*.,[6] and Zhang *et al*.[14] Cohn *et al*.,[5] in their case series of 11 patients, assessed the outcome of plasmin mediated vitrectomy and membrane peeling, and demonstrated an improvement in vision in almost two-thirds of cases. Bruè *et al*.[4] have illustrated utility of microperimetry in demonstrating low retinal sensitivity at the site of epriretinal adhesion and thereby concluding that surgical intervention should be considered in patients with CHRRPE before the worsening of retinal sensitivity.

The common indication for surgical intervention in all of the abovementioned reports with good visual outcomes was the recent onset visual loss that could be attributed to vitreoretinal distortion secondary to contraction of epiretinal component associated with CHRRPE. Our study shows that the surgical intervention, which primarily is done for vitreoretinal interface changes, leads to a limited improvement in younger age group. The plausible reason for poor outcome in such patients could be preexisting amblyopia, which may not be the contributing factor in older patients who had good visual outcome. In addition, we noted that the preretinal fibrosis appears to be one of the distinct characteristics, which differentiates between good visual outcome group and poor visual outcome. Preretinal fibrosis accounted for inner retinal changes such as maxi peaks and mini peaks as well.

Limitations of our study include small sample size and poor ophthalmic follow-up, documentation of progressive vision loss before surgical intervention, and lack of data for long-term follow-up (>1 year). Due to small sample size, we could not to establish the possible predictors for visual outcomes postsurgical intervention. We could not assess the role of amblyopia in our subjects due to lack of previous ophthalmic history.

Conclusion

Outcome of surgical intervention appears to be good in eyes with preretinal fibrosis. However, the OCT indicators of visual recovery such as retinal thickness and outer retinal structural integrity, seen following surgical removal of ERM,[15,16] fails to explain the visual outcome in CHRRPE. Natural history of the disease in addition to longer follow-up after surgical intervention would further expand our understanding to improvise the treatment outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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