Scan code to view VIDEO

COMBINED HAMARTOMA OF THE RETINA AND RETINAL PIGMENT EPITHELIUM AT PEDIATRIC AGE

Surgical Versus Conservative Approach

SENGUL OZDEK, MD, FEBO, FASRS,* AHMET YUCEL UCGUL, MD, FICO, FEBO,*†
M. ELIZABETH HARTNETT, MD, FACS, FARVO,‡ MUBERRA AKDOGAN, MD,§ PARVEEN SEN, MS,¶
MUNA BHENDE, MS,¶ CAGRI GIRAY BESIRLI,MD,PHD,** MURAT KARACORLU,MD,MSC, FEBO,††
VAIDEHI DEDANIA, MD,‡‡ BARBARA PAROLINI, MD,§§ SANGEET MITTAL, MD,¶¶
ALAY BANKER, MD,*** EHAB EL RAYES, MD, PHD,††† MOHAMED TAWFIK, MD, FRCSED,‡‡‡
WEI-CHI WU, MD, PHD,§§§ YAMINI ATTIKU, MD,¶ ERIC HANSEN, MD,‡ DAVID PORTNEY, BS,**
CHINTAN SARVAIYA, MD,*** OZLEM SAHIN, MD,¶¶¶
HUSEYIN BARAN OZDEMIR, MD, FICO, FEBO,* GOKHAN GURELIK, MD*

Purpose: To report outcomes of pediatric patients with combined hamartoma of the retina and the retina pigment epithelium followed up conservatively or after pars plana vitrectomy.

Methods: This retrospective multicenter study included 62 eyes of 59 pediatric patients with combined hamartoma of the retina and the retina pigment epithelium from 13 different international centers with an average age of 7.7 ± 4.7 (0.3–17) years at the time of the diagnosis and having undergone pars plana vitrectomy or followed conservatively. At baseline and each visit, visual acuity values, optical coherence tomography for features and central foveal thickness, and tumor location were noted. Lesions were called as Zone 1, if it involves the macular and peripapillary areas, and the others were called as Zone 2 lesions.

Results: Twenty-one eyes of 20 patients in the intervention group and 41 eyes of 39 patients in the conservative group were followed for a mean of 36.2 ± 40.4 (6–182) months. Best-corrected visual acuity improved in 11 (68.8%) of 16 eyes in the intervention group and 4 (12.9%) of 31 eyes in the conservative group ($P < 0.001$). The mean central foveal thickness decreased from 602.0 ± 164.9 μm to 451.2 ± 184.3 μm in the intervention group, while it increased from 709.5 ± 344.2 μm to 791.0 ± 452.1 μm in Zone 1 eyes of the conservative group. Posterior location of tumor, irregular configuration of the foveal contour and ellipsoid Zone defect in optical coherence tomography, subretinal exudate and prominent vascular tortuosity were associated with poor visual acuity.

Conclusion: Vitreoretinal surgery is safe and effective in improving vision and reducing retinal distortion in Zone 1 combined hamartoma of the retina and the retina pigment epithelium in children.

RETINA 43:338–347, 2023

The combined hamartoma of the retina and the retinal pigment epithelial (CHRRPE), first described by Gass, is characterized by a hamartoma of the neurosensory retina and retina pigment epithelium with overlying glial cell proliferation often leading to retinal pucker and distortion.[1] The common clinical signs of CHRRPE are an elevated mass (80%), pigmentation (87%), vascular tortuosity (93%), and epiretinal membrane (ERM) formation (78%).[2] Combined hamartoma of the retina and the retinal pigment epithelial tends to be located in the posterior pole and is unilateral, although lesions associated with neurofibromatosis Type 1 or 2 can present with bilateral involvement.[3,4] Vision can be affected at different rates depending on the tumor location. The main symptoms of patients with CHRRPE include vision

loss, strabismus, floaters, metamorphopsia, and leukocoria. However, some asymptomatic patients can be diagnosed with CHRRPE during routine ophthalmic examinations. Complications such as tractional retinal detachment, vitreous and retinal hemorrhage, choroidal neovascularization, retinal hole, or retinoschisis have been reported in patients with CHRRPE.[5–7]

Although the generally accepted indications for surgical treatment of CHRRPE include the presence of ERM causing macular distortion and development of tractional retinal detachment, there is no consensus on which cases should be treated surgically or conservatively. Some clinicians adopted early vitrectomy and membrane peeling for removal of ERM in patients with CHRRPE,[8] whereas others followed patients without surgical intervention unless marked macular distortion, tractional retinal detachment, or vitreous hemorrhage developed.[9]

There are few studies with large sample sizes that reported longitudinal data from patients with CHRRPE, and most presented conservative follow-up highlighting gradual decreases in visual acuity.[2,9,10] The remainder of studies are small case series or case reports of patients with wide age ranges from four months to 66 years. No previous study evaluated the characteristics and outcomes of CHRRPE in pediatric patients only. Several case series with small sample sizes reported favorable outcomes after pars plana vitrectomy (PPV) of CHRRPE.[8,11–14]

In this article, we conducted a multicenter international collaborative retrospective study of outcomes in pediatric patients with CHRRPE based on management choice, tumor location and characteristics, and age at diagnosis.

Material and Methods

This retrospective multicenter collaborative study was conducted in accordance with the Declaration of Helsinki and approved by the Gazi University Research Ethics Committee (Approval No: 2020/105). Each site obtained local permissions from their Human Subjects Boards.

Patient Population

Pediatric patients younger than 18 years diagnosed with CHRRPE were included from 13 different international centers. Patients were excluded if they had a history of ocular trauma, inflammatory disease, subretinal scarring and fibrosis, or a follow-up of less than 6 months. Patients were divided into two groups based on whether they had conservative management (conservative group) or PPV and ERM removal (intervention group). When possible, patients underwent genetic testing for neurofibromatosis, neurofibromatosis Type-1, and neurofibromatosis Type-2, if not already known.

Surgical Technique

In patients in the intervention group, general steps for the surgery were as follows: 1) After the placement of trocars at pars plana, core vitrectomy was performed; 2) posterior hyaloid was detached and ERM was removed by using forceps; 3) the internal limiting membrane (ILM) was also peeled in most cases (95.3%) (see **Video**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B828, which demonstrates the peeling of ERM and ILM); and 4) after limited vitreous base cleaning and peripheral retina control, a vitreous tamponade (air, C_3F_8, SF_6, or silicone oil) was used if needed according to surgeons' discretion at the end of the procedure.

Data Collection and Outcomes

Medical data were collected onto uniform data sheets and included patient symptoms, presence of systemic diseases, including neurofibromatosis, and type of management (conservative or intervention). In children who were able to be measured, best-corrected Snellen visual acuity converted to logMAR equivalent best-corrected

From the *Department of Ophthalmology, Gazi University, School of Medicine, Ankara, Turkey; †Department of Ophthalmology, Ahi Evran University, Training and Research Hospital, Kırşehir, Turkey; ‡John A. Moran Eye Center, University of Utah, Salt Lake City, Utah; §Department of Ophthalmology, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyon, Turkey; ¶Sankara Nethralaya, Chennai, Tamil Nadu, India; **Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan; ††Istanbul Retina Institute, Istanbul, Turkey; ‡‡Langone Eye Center, NYU School of Medicine, New York, New York; §§Eyecare Clinic, Brescia, Italy; ¶¶Thind Eye Hospital in Model Town, Jalandhar, India; ***Banker's Retina Clinic and Laser Centre, Navrangpura, Ahmedabad, India; †††Research Institute of Ophthalmology, Cairo, Egypt; ‡‡‡Memorial Institute of Ophthalmological Research, Giza, Egypt; §§§Department of Ophthalmology, Chang Gung Memorial Hospital, Taoyuan, Taiwan; and ¶¶¶Department of Ophthalmology, Marmara University Hospital, Istanbul, Turkey.

This work was supported by the National Institutes of Health EY014800 and an Unrestricted Grant from Research to Prevent Blindness, Inc, New York, NY, to the Department of Ophthalmology & Visual Sciences, University of Utah; and the National Institutes of Health R01EY015130 and R01EY017011 to M.E.H.

None of the authors has any financial/conflicting interests to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

It is to specifically state "No Competing interests are at stake and there is No Conflict of Interest" with other people or organizations that could inappropriately influence or bias the content of the paper.

Reprint requests: Sengul Ozdek, MD, FEBO, FASRS, Ophthalmology Department, Gazi University School of Medicine, Besevler, 06500 Ankara, Turkey; e-mail: sozdek@gazi.edu.tr

visual acuity (BCVA) and central foveal thickness (CFT) and prominent ellipsoid zone defects on optical coherence tomography (OCT) were measured at the initial and final examinations. Descriptive fundus findings included presence of subretinal exudates, prominent vascular tortuosity, and lesion size by area and location. The lesion sizes were assessed on color images by the surgeons and qualitatively assessed for size differences during the follow-up period (areas became bigger, smaller, or stayed the same). Combined hamartoma of the retina and the retinal pigment epithelial lesions were classified based on previous reports.[15] Lesions in Zone 1 involved the macular and peripapillary areas, whereas lesions in Zone 2 were outside the macular and peripapillary areas and involved the peripheral retina.

Age at diagnosis of CHRRPE, data of fundus findings, tumor location, OCT, and imaging features were expressed as means ± SD for numeric variables and number (percentage) for categorical variables. Change in CFT and BCVA between initial and final examinations were determined and analyzed between the conservative and intervention groups. Children aged 7 years and younger received amblyopia treatment in both groups. The age at the time of diagnosis, either 7 years or younger or older than 7 years, was evaluated for effect on outcome in each group.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences for Windows (version 22.0, SPSS, Chicago, IL). Skewness and kurtosis values were examined for the normality test. Numeric variables were considered to show parametric distribution when the kurtosis and skewness values of them were between −1.5 and +1.5.[16] The Independent samples *T*-test or Mann–Whitney *U* test was used to compare numeric clinical characteristics of patients at baseline and final visits. Chi-square test or Fisher exact test were performed to compare the categorical clinical characteristics of patients including lesion size, lesion location, OCT findings, and fundus findings, at baseline and final visit. Z test and adjusted standardized residual values were used to calculate *P* values for post hoc analysis of these categorical data. The Bonferroni post hoc test was used to control for Type I error. The split-plot analysis of variance was used to compare changes in BCVA and CFT during the follow-up between the groups. The influence of the variables on visual improvement was evaluated using multivariate logistic regression analysis. A *P* value ≤0.05 was considered as statistically significant.

Results

Baseline demographic and clinical characteristics of the patients for both groups are summarized in Table 1. A total of 62 eyes of 59 patients with CHRRPE were enrolled in this study. Twenty-one eyes (33.9%) of 20 patients underwent PPV, whereas 41 eyes (66.1%) of 39 patients were followed conservatively. The average age at diagnosis was 7.7 ± 4.7 (0.3–17) years, and the mean follow-up was 36.2 ± 40.4 (6–182) months. Four patients had a history of neurofibromatosis Type-1, and nine patients had a history of neurofibromatosis Type-2. Three patients (5.1%) had bilateral involvement, and all of them were diagnosed with neurofibromatosis Type-1 or neurofibromatosis Type-2. The main initial symptom was diminution of vision (62.9%), followed by strabismus (19.4%).

Functional Outcomes Assessed by Management

Best-corrected visual acuity was measurable in 47 eyes (75.8%). The mean initial BCVA was 1.01 ± 0.69 (Snellen equivalent, 20/204) and was not different between the intervention and the conservative groups (Table 1). Best-corrected visual acuity increased in 11 (68.8%) of 16 eyes in the intervention group (Figure 1) but only in 4 (12.9%) of 31 eyes in the conservative group ($P = 0.001$). The initial mean BCVA in the intervention group increased significantly from 1.06 ± 0.41 (Snellen equivalent, 20/229) at baseline to 0.65 ± 0.55 logMAR (Snellen equivalent, 20/89) at the final follow-up ($P = 0.001$, Table 2). However, there was no significant change in BCVA (0.98 ± 0.79 [Snellen equivalent, 20/190] at baseline, 0.91 ± 0.64 logMAR [Snellen equivalent, 20/162] at final) in the conservative group ($P = 0.881$). Patients aged 7 years or younger received amblyopia therapy in both groups and made up 76.1% in the intervention group and 58.5% in the conservative group (Table 2).

Anatomical Outcomes and Outcomes by Location

Optical coherence tomography information was available in 36 eyes (58.1%). The mean baseline CFT was 636.4 ± 327.9 μm; there was no significant difference in baseline CFTs between the intervention (614.6 ± 130.7 μm) and conservative (643.0 ± 370.0 μm) groups. The mean final CFT decreased from 614.6 to 427.3 ± 174.9 μm in the intervention group but increased from 643 to 727.8 ± 463.4 μm in the conservative group ($P = 0.001$).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients With CHRRPE

	Intervention Group	Conservative Group	Total	*P*
Number of eyes (n, %)	21 (33.9%)	41 (66.1%)	62	
Mean age at presentation (years)	5.9 ± 4.8 (0.3–17)	8.5 ± 4.6 (0.3–16)	7.7 ± 4.7 (0.3–17)	0.052*
Mean follow-up time (month)	26.7 ± 30.2 (6–98)	43.9 ± 46.2 (6–182)	36.2 ± 40.4 (6–182)	0.141†
Female (n, %)	11 (52.4%)	14 (34.1%)	25 (40.3%)	0.117‡
Bilaterality (n, %)	1 (5.0%)	2 (5.1%)	3 (5.1%)	0.964§
Mean baseline BCVA (logMAR) Snellen equivalent	1.06 ± 0.41 [20/229]	0.98 ± 0.79 [20/190]	1.01 ± 0.69	0.703*
Mean baseline CFT (μm)	614.6 ± 130.7	643.0 ± 370.0	636.4 ± 327.9	0.834*
95% CI	[487.1–804.8]	[495.2–1,048.7]		
Main first sign and symptom				0.402‡
Strabismus	4 (19.0%)	8 (19.5%)	12 (19.4%)	
Vision loss	15 (71.4%)	24 (58.5%)	39 (62.9%)	
None (asymptomatic)	2 (9.5%)	9 (22.0%)	11 (17.7%)	
Location				**0.015**‡
Zone 1	21 (100%)	31 (75.6%)	52 (83.9%)	
Zone 2	—	10 (24.4%)	10 (16.1%)	
Associations				0.324‡
Neurofibromatosis Type-1	2 (9.5%)	2 (4.9%)	4 (6.5%)	
Neurofibromatosis Type-2	1 (4.8%)	8 (19.5%)	9 (14.5%)	

Bold values indicate statistical significance.
*Independent samples *T*-test.
†Mann–Whitney *U* test.
‡Chi-square test.
§Fisher exact test.
CI, confidence interval; NF, neurofibromatosis.

Combined hamartoma of the retina and the retinal pigment epithelial was located in Zone 1 in 83.9% and in Zone 2 in 16.1%. All lesions were located in Zone 1 in the intervention group, whereas 75.6% were located in Zone 1 in the conservative group ($P = 0.013$). All lesions located in Zone 2 (16.1%) were monitored conservatively. The best-corrected visual acuity remained stable at 0.05 ± 0.06 in eyes with Zone 2 involvement in the conservative group. The best-corrected visual acuity of eyes with Zone 1

Table 2. Final Outcomes of the Patients With CHRRPE

	Intervention Group n:21	Conservative Group n:41	*P*
Eyes with an increase in BCVA*	11/16 (68.8%)	4/31 (12.9%)	<**0.001**†
Eyes with a decrease in BCVA*	1/16 (6.2%)	1/31 (3.2%)	0.570‡
Eyes having at least ambulatory vision* (logMAR≤1.7, Snellen ≥20/1,000)	14/16 (87.5%)	24/31 (77.4%)	0.436†
Mean final BCVA (logMAR) Snellen equivalent	0.65 ± 0.55 [20/89]	0.91 ± 0.64 [20/162]	0.232§
Mean final CFT (μm)	427.3 ± 174.9 [222.3–680.1]	727.8 ± 463.4 [513.1–1,068.9]	0.105¶
95% CI			
Eyes receiving amblyopia treatment (n, %)	16 (76.2%)	24 (58.5%)	0.281†
Complications			
Rhegmatogenous retinal detachment	1 (4.7%)	—	NA
Hypotonia	1 (4.7%)	—	NA

Bold values indicate statistical significance.
*Not available in patients of preverbal ages.
†Chi-square test.
‡Fisher exact test.
§Mann–Whitney *U* test.
¶Independent samples *T*-test.
CI, confidence interval; NA, not applicable.

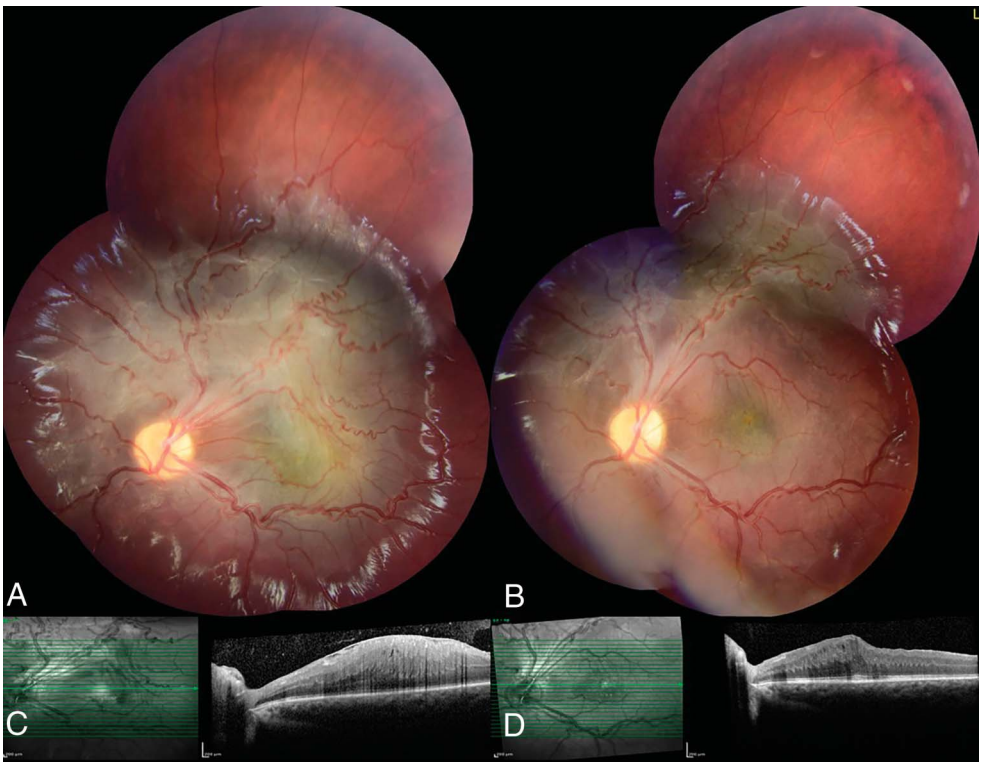

Fig. 1. Representative images of a patient with CHRRPE who underwent PPV and membrane peeling surgery. **A.** Preoperative color fundus photo demonstrates the presence of CHRRPE located in the macula in a 7-year-old girl. **B.** Note the decrease in retinal distortion a year after vitreoretinal surgery. **C.** Preoperative optical coherence tomography image shows the ERM and CHRRPE lesion of the macula. **D.** Note the flattening of the macula and intact ellipsoid zone a year after surgery. Best-corrected visual acuity improved from 20/200 at baseline to 20/60 at final.

involvement significantly improved from 1.04 ± 0.34 logMAR (Snellen equivalent, 20/219) at baseline to 0.55 ± 0.40 logMAR (Snellen equivalent, 20/70) at the final examination in the intervention group, whereas it slightly improved from 1.10 ± 0.73 (Snellen equivalent, 20/251) to 0.99 ± 0.62 (Snellen equivalent, 20/195) in the conservative group (P = 0.003) (Figure 2-left). In addition, in eyes with Zone 1 involvement, the mean CFT decreased from 614.6 ± 130.7 μm to 427.3 ± 174.9 μm in the intervention group, whereas it increased from 709.5 ± 344.2 μm to 791.0 ± 452.1 μm in the conservative group (P = 0.001) (Figure 2-right).

Change in Size of the Lesion

Change in the size of lesions was determined in 41 eyes that had baseline and final color fundus images. At the follow-up visit, 9 lesions (21.9%) were assessed as having smaller areas, 26 lesions (63.4%) as having the same areas, and 6 lesions (14.6%) as having larger areas. In the intervention group, 7 lesions (36.8%) were assessed as smaller, 11 (57.9%) the same, and 1 (2.4%) larger. In the conservative group, 2 lesions (9.1%) were assessed as smaller, 15 (68.2%) the same, and 5 (22.7%) larger (Figure 3) (P = 0.044).

Age of Patients at Presentation

Thirty-eight (64.4%) of the patients were 7 years or younger with 15 (75.0%) in the intervention group and 23 (59.0%) in the conservative group (P = 0.311). Strabismus was more common (27.8%) in patients 7 years or younger than in those >7 (8.6%) (Table 3). In general, age at presentation did not have a significant effect on BCVA or CFT, regardless of being in the intervention or conservative groups. The distribution of involvement was similar in both age groups (P = 0.351). The mean BCVA improved from 1.17 ± 0.71 logMAR (Snellen equivalent, 20/295) at baseline to 0.85 ± 0.68 logMAR (Snellen equivalent, 20/141) at final in those 7 years or younger and from 0.90 ± 0.54 (Snellen equivalent, 20/158) to 0.73 ± 0.55 logMAR (Snellen equivalent, 20/107) in those 7 years or older (Figure 4-left). The mean CFT decreased from 807.2 ± 434.4 μm to 769.1 ± 480.4 μm in children 7 years or older and decreased from 543.6 ± 146.6 μm to 486.2 ± 121.9 μm in those 7 years or younger (Figure 4-right). Change in lesion size was similar in patients 7 years or younge and 7 years or older (Table 3).

Eyes with favorable (Snellen >20/200) and unfavorable (≤20/200) final BCVAs were further analyzed according to baseline lesion characteristics. Zone 2 involvement was found to be more frequent in eyes with favorable final BCVA compared with those with

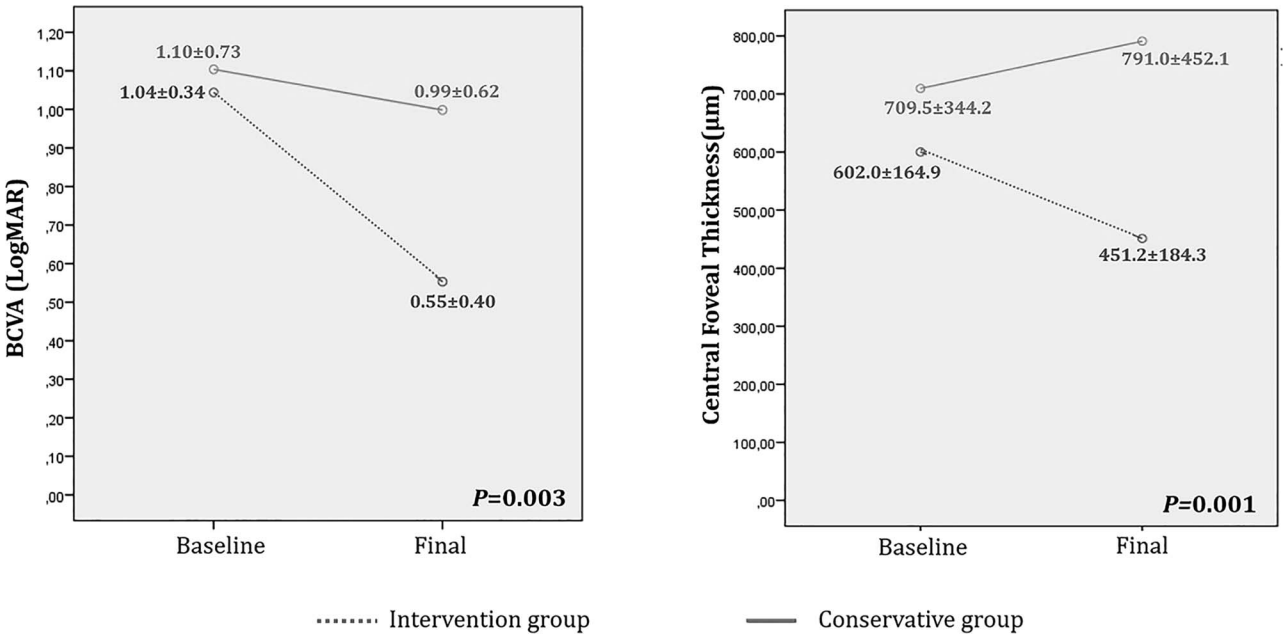

Fig. 2. Change in BCVA and CFT from baseline to final in patients with Zone 1 located CHRRPE in the intervention and conservative groups. Split-plot analysis of variance test. Note that BCVA and CFT improved more in patients with Zone 1-located CHRRPE undergoing surgery, compared with those monitored conservatively.

unfavorable BCVAs ($P = 0.050$). The presence of subretinal exudates, prominent vascular tortuosity, and severe ellipsoid zone defects on OCT were found to be more common in eyes with unfavorable BCVAs ($P = 0.002$, 0.044, and <0.001, respectively, Table 4).

Multivariate logistic regression analysis revealed significant associations between having surgery and visual improvement (odds ratio [OR] 6.986 [95% confidence interval 3.223 to 18.671]; ***P* < 0.001**) and between baseline BCVA and visual improvement (odds ratio 2.125 [95% confidence interval 0.406–9.504]; ***P*= 0.045**) (Table 5).

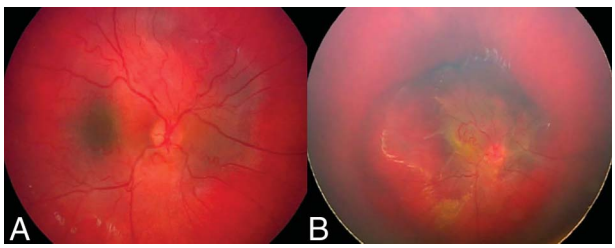

Fig. 3. Representative images of a patient with peripapillary CHRRPE in the conservative group. **A.** Color fundus photo demonstrates the presence of peripapillary CHRRPE located in the nasal peripapillary area in a 3-year-old boy at presentation. **B.** Note the increase in lesion size to involve the macula, retinal distortion, and pigmentation within 3 years of follow-up. Best-corrected visual acuity remained at counting fingers level in spite of amblyopia treatment during the follow-up.

Surgical Technique-Related Outcomes and Complications

Besides PPV surgery, ERM and ILM peeling was performed in all but one eye. Considering the intraoperative complications, dot like superficial retinal hemorrhages were observed in all cases, all of which resolved without any sequela within postoperative one month. A small extrafoveal residue of ERM was left in two cases because of the firm adhesion between the retina and ERM. Iatrogenic retinal tear developed in two eyes (9.4%), at the superior part of macula and at the nasal retina during ERM peeling, both of which were lasered and tamponaded with either silicone oil or C3F8 gas. BSS was used in five eyes, air in 11 eyes, and SF_6 in three eyes as a tamponade. One patient (4.7%) with iatrogenic retinal tear developed proliferative vitreoretinopathy and hypotony, and resulted in a vision of light perception only.

Discussion

The visual prognosis during the natural course of CHRRPE is not known well, with only several reports in the literature. In 1984, Schachat et al[2] from the Macula Society Research Committee evaluated 41 patients aged between 10 months and 66 years with a mean follow-up of 4 years in a multicenter study. They reported 3 (8%) of 38 patients who received only amblyopia therapy showed visual improvement,

Table 3. Baseline Characteristics of the Patients With CHRRPE According to Age

	≤7 Years of Age	>7 Years of Age	*P*
Number of patients (n, %)	36 (61.0%)	23 (38.9%)	
Mean baseline BCVA (lLogMAR) (n = 47) Snellen equivalent	1.17 ± 0.71 [20/295]	0.90 ± 0.54 [20/158]	0.130*
Mean baseline CFT (μm) (n = 36)	543.6 ± 146.6	807.2 ± 434.4	**0.028**†
Main first symptom			**0.020**‡
Strabismus	10 (27.8%)	2 (8.6%)	
Vision loss	18 (50.0%)	19 (82.6%)	
None (asymptomatic)	8 (22.2%)	2 (8.6%)	
Location (n = 62 eyes)			0.351‡
Zone 1	31 (81.6%)	21 (87.5%)	
Zone 2	7 (18.4%)	3 (12.5%)	
Size (n = 42 eyes)			0.482‡
Got smaller	6 (25.0%)	3 (16.7%)	
Stable	13 (54.2%)	13 (72.2%)	
Got bigger	5 (20.8%)	2 (11.1%)	

Bold values indicate statistical significance.
*Independent samples *T*-test.
†Mann–Whitney *U* test.
‡Chi-square test.

whereas one (33%) of the remaining three patients who underwent vitreoretinal surgery had improved final visual acuity. Furthermore, they reported a decrease in visual acuity in 10 (24.3%) of 41 patients. Shields et al[9] evaluated 77 patients with CHRRPE with a mean age of 11.9 years (0.4–60 years) in a single-center study and reported that only 4 patients (5%) who had macular CHRRPE causing distortion or vitreous hemorrhage underwent vitreoretinal surgery and two of them showed visual improvement after the surgery at a mean follow-up of 26 months. Moreover, in conservatively managed patients, they reported a visual acuity loss of ≥3 Snellen lines in 60% with macular involvement and 13% with extramacular involvement. The authors emphasized that the gradual decrease in visual acuity in patients with CHRRPE followed up conservatively was an expected result. Dedania et al[15] reported that none of the eight

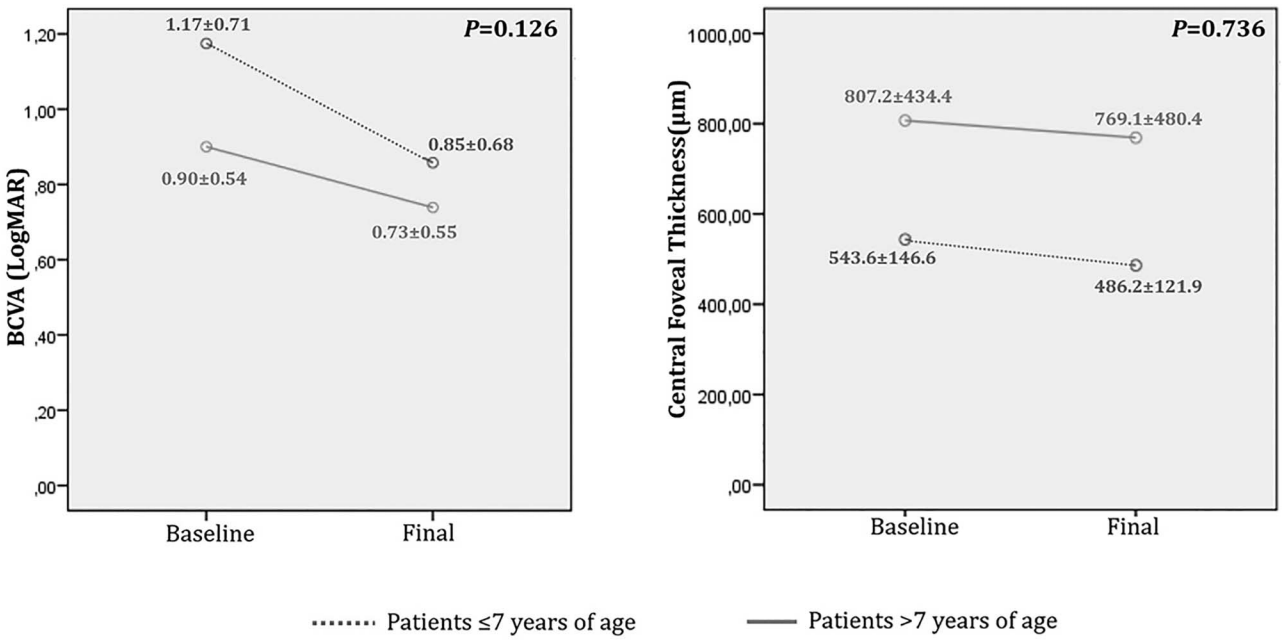

Fig. 4. Change in BCVA and CFT from baseline to final with respect to patients' age. Split-plot analysis of variance test. Both BCVA and CFT similarly changed in both patients >7 and ≤7 years of age.

Table 4. CHRRPE Characteristics of the Patients According to Final Visual Outcome

	Final BCVA >20/200 n:30	Final BCVA ≤20/200 n:17	Total	*P*
Lesion location				**0.050***
Zone 1	23 (57.5%)	17 (42.5%)	40	
Zone 2	7 (100%)	—	7	
Lesion size with time (n:33)				0.529*
Remained stable	15 (50%)	8 (47.1%)	23 (69.7%)	0.846†
Enlarged	2 (6.7%)	2 (11.7%)	4 (12.1%)	0.547†
Became smaller	5 (16.7%)	1 (5.9%)	6 (18.2%)	0.287†
Fundus findings				**0.033***
Epiretinal membrane	26 (86.7%)	16 (94.1%)	42 (89.4%)	0.426†
Vascular tortuosity	11 (36.7%)	11 (64.7%)	22 (46.8%)	**0.044**†
Pigmentary changes	9 (30%)	3 (17.6%)	12 (25.5%)	0.351†
Subretinal exudate	—	5 (29.4%)	5 (10.6%)	**0.002**†
Tractional retinal detachment	4 (13.3%)	1 (5.9%)	5 (10.6%)	0.426†
OCT—fovea (n:36)				**0.019***
Normal	9 (30%)	—	9 (25%)	**0.012**†
Flat	1 (3.3%)	2 (11.7%)	3 (8.3%)	0.256†
Bumpy	13 (43.3%)	11 (64.7%)	24 (66.7%)	0.159†
OCT—ellipsoid zone defect (n:36)				**0.018***
Normal	15 (50%)	3 (17.6%)	18 (38.3%)	**0.028**†
Mild	4 (13.3%)	—	4 (8.5%)	0.115†
Moderate	2 (6.7%)	1 (5.9%)	3 (6.4%)	0.916†
Severe	2 (6.7%)	9 (52.9%)	11 (23.4%)	<**0.001**†

Bold values indicate statistical significance.
*Chi-square test.
†Calculated *P* values after post hoc analysis of categorical data.
N/A, not applicable.

eyes with CHRRPE had vision loss during 7 years of follow-up and two eyes that received amblyopia treatment had vision increase. In the conservative group of this study, an increase in vision was observed in 4 eyes (12.9%) potentially due to amblyopia management. In patients with progressive retinal distortion, vision improvement with amblyopia therapy might mislead one into thinking the condition is stable despite the progression of anatomical deterioration. Therefore, fundus evaluation, including possible OCT imaging, is important in these patients.

Location of the Tumor

The effect of lesion location on visual prognosis in patients with CHRRPE has previously been evaluated in studies with large patient populations. Schachat et al[2] reported that lesions located around or within the

Table 5. Multivariate Logistic Regression Analysis Shows the Association Between Visual Improvement and Possible Clinical Predictors in Patients With CHRRPE

Multivariate Logistic Regression Analysis	*P*	Odds Ratio	95% of CI for Odds Ratio	
			Lower	Upper
Age (categorical) 7 years or younger 7 years or older	0.548	0.361	0.052	2.915
Sex (categorical) Male Female	0.777	0.080	0.011	0.929
Treatment type (categorical) Observation Surgery	<**0.001**	6.986	3.223	18.671
Baseline BCVA (categorical) ≤20/200 >20/200	**0.045**	2.125	0.406	9.504

Patients having undergone surgery and those with a baseline BCVA of >20/200 are more likely to show visual improvement. Bold values indicate statistical significance.

optic disc, papillomacular bundle, or fovea experienced vision loss. They also emphasized that extramacular CHRRPEs caused vision loss by developing ERMs that extended to the macula. Although it is assumed that central vision is preserved in peripheral CHRRPEs that do not threaten the macula, Lazzarini et al[7] reported vision loss in a patient with a peripapillary choroidal neovascular membrane who was followed up for a peripheral CHRRPE. Gupta et al[17] reviewed 50 patients with CHRRPE and reported that patients with peripapillary involvement had better visual acuity (0.50 ± 0.42 logMAR [Snellen equivalent, 20/63] vs. 1.34 ± 1.18 logMAR [Snellen equivalent, 20/302]) compared with those with macular involvement. Similarly, Shields et al[9] reported that 36% of the patients with poor vision had macular involvement, compared with 12% with juxtapapillary lesions. We preferred to classify the peripapillary and macular lesions in the same category as "posterior pole lesions" and referred to them as Zone 1 lesions in this study because it is not always possible to distinguish CHRRPE lesions as only having peripapillary or macular involvement; lesions can involve both regions. In addition, posterior pole lesions are the ones that affect vision more than peripheral lesions. All eyes with final BCVAs of <1 logMAR (>20/200 Snellen) had Zone 1 lesions in tis study.

Lesion Characteristics

Previously, clinicians compared lesion characteristics at different locations to attempt to predict the prognosis of CHRRPE. Shields et al[9] evaluated the lesion characteristics of macular and extramacular tumors and reported that exudation, fibrosis, and foveal dragging were more common in patients with macular involvement, whereas optic disc dragging was more common in patients with extramacular involvement. Gupta et al[17] found that ellipsoid zone defect, RPE disruption, and choroidal neovascular membrane development were more frequent in peripapillary CHRRPEs, although BCVA was better in patients with peripapillary CHRRPE compared with those with macular CHRRPE. In this study, unlike the other studies, we evaluated the relationship between the baseline tumor characteristics and the final vision. Defects of the ellipsoid zone on OCT, lesions with more subretinal exudates and vascular tortuosity were more often associated with poor final BCVAs.

Surgical Outcomes

Most large-scale studies include patients followed conservatively. Surgical data are usually restricted to smaller series and case reports. The largest series by Sun et al[8] included 15 patients treated with PPV. They reported visual improvement in 14 eyes (93%). Another report of outcomes after PPV in 14 pediatric patients found improved vision in 11 patients.[11] Other case reports found either an increase or no change in vision after PPV surgery [14,18]. This study is the only study that compared the visual results of patients with Zone 1-located CHRRPE either followed up conservatively or treated surgically and revealed that visual improvement was significantly more pronounced in surgically treated patients. This study suggests that functional improvement can be obtained in eyes with Zone 1 lesions after PPV than in eyes followed up conservatively with short-term follow-up. Surgical technique is not complicated, however, ERM is more adherent and thicker than idiopathic ERM which resulted in iatrogenic retinal break formation during membrane peeling in 9.4% of the cases. Amblyopia treatment was also believed to help in improvement of vision which was applied for all children younger than 8 years both in the intervention and the conservative groups.

Lesion Size

To the best our knowledge, there are no data on the change in size of the lesion during the course of follow-up. In this study, all imaged lesions were qualitatively assessed for changes in size from the initial to follow-up examinations. Because it is difficult to distinguish the tumor itself from the associated ERM, the size of the combined lesion was determined. Including both groups, 14.6% of the lesions increased, 63.4% remained stable, and 21.9% became smaller during the follow-up as reported by each author. More lesions became smaller in the intervention group (36.8%) compared with the conservative group (9.1%) and may be due to removal of epiretinal glial proliferation in surgery.

To the best of our knowledge, this is the first multicenter study comparing eyes of pediatric patients with CHRRPE followed up conservatively or treated surgically and being the largest series of surgically treated cases. Limitations of this study include the retrospective design, unavailability of OCT and imaging in some of the cases and visual acuity in preverbal children. Moreover, we could not statistically analyze the effect of tamponade used and the addition of ILM peeling on anatomical and functional outcomes due to the limited number of cases without ILM peeling.

In conclusion, our study supports that, vitreoretinal surgery is safe and effective for selected Zone 1 lesions which results in improvement in vision. A conservative approach is suggested for lesions outside

the posterior pole. Amblyopia treatment may improve vision in all eyes with posterior pole lesions either treated surgically or conservatively. Posterior location of tumor, irregular configuration of the foveal contour and the presence of ellipsoid zone defects in OCT, subretinal exudate, and prominent vascular tortuosity were associated with poor visual outcomes in this study.

Key words: combined hamartoma of the retina and the retina pigment epithelium, pediatric age, pars plana vitrectomy, retina, retinal pigment epithelium, surgery, amblyopia treatment.

References

1. Gass JDM. An unusual hamartoma of the pigment epithelium and retina simulating choroidal melanoma and retinoblastoma. Retina (Philadelphia, PA) 2003;23:171–183. discussions 184–175.
2. Schachat AP, Shields JA, Fine SL, et al. Combined hamartomas of the retina and retinal pigment epithelium. Ophthalmology 1984;91:1609–1615.
3. Yassin SA, Al-Tamimi ER. Familial bilateral combined hamartoma of retina and retinal pigment epithelium associated with neurofibromatosis 1. Saudi J Ophthalmol 2012;26:229–234.
4. Firestone BK, Arias JD, Shields CL, Shields JA. Bilateral combined hamartomas of the retina and retinal pigment epithelium as the presenting feature of neurofibromatosis type 2 (wishart type). J Pediatr Ophthalmol Strabismus 2014;51:e33–e36.
5. Schachat AP, Glaser BM. Retinal hamartoma, acquired retinoschisis, and retinal hole. Am J Ophthalmol 1985;99:604–605.
6. Kahn D, Goldberg MF, Jednock N. Combined retinal-retina pigment epithelial hamartoma presenting as a vitreous hemorrhage. Retina 1984;4:40–43.
7. Lazzarini TA, Al-Khersan H, Patel NA, et al. Peripheral combined hamartoma of the retina and retinal pigment epithelium with remote peripapillary choroidal neovascular membrane. Am J Ophthalmol Case Rep 2020;20:100954.
8. Sun LS, Raouf S, Rhee D, Ferrone PJ. Surgical outcomes of epiretinal membrane removal due to combined hamartoma of the retina and RPE. Ophthalmic Surg Lasers Imaging Retina 2020;51:546–554.
9. Shields CL, Thangappan A, Hartzell K, et al. Combined hamartoma of the retina and retinal pigment epithelium in 77 consecutive patients. Ophthalmology 2008;115:2246–2252.e3.
10. Ledesma-Gil G, Essilfie J, Gupta R, et al. Presumed natural history of combined hamartoma of the retina and retinal pigment epithelium. Ophthalmol Retina 2021;5:1156–1163.
11. Cohn AD, Quiram PA, Drenser KA, et al. Surgical outcomes of epiretinal membranes associated with combined hamartoma of the retina and retinal pigment epithelium. Retina 2009;29:825–830.
12. Sanchez-Vicente JL, Rueda-Rueda T, Llerena-Manzorro L, et al. Surgical treatment in combined hamartoma of the retina and retinal pigment epithelium. Archivos de la Sociedad Española de Oftalmología (English Edition) 2017;92:137–140.
13. Vinekar A, Quiram P, Sund N, et al. Plasmin-assisted vitrectomy for bilateral combined hamartoma of the retina and retinal pigment epithelium: histopathology, immunohistochemistry, and optical coherence tomography. Retin Cases Brief Rep 2009;3:186–189.
14. Xiao Z, Fangtian D, Rongping D, Weihong Y. Surgical management of epiretinal membrane in combined hamartomas of the retina and retinal pigment epithelium. Retina 2010;30:305–309.
15. Dedania VS, Ozgonul C, Zacks DN, Besirli CG. Novel classification system for combined hamartoma of the retina and retinal pigment epithelium. Retina 2018;38:12–19.
16. Tabachnick B, Fidell L. Using Multivariate Statistics. Boston, MA: 6th Pearson Education. Inc; 2013. [Google Scholar].
17. Gupta R, Fung AT, Lupidi M, et al. Peripapillary versus macular combined hamartoma of the retina and retinal pigment epithelium: imaging characteristics. Am J Ophthalmol 2019;200:263–269.