

Combined Hamartoma of the Retina and Retinal Pigment Epithelium at Pediatric Age: Surgical versus Conservative Approach

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Summary statement: This multicenter study demonstrates that pars plana vitrectomy with membrane peeling results in more favorable visual and anatomical outcomes compared to observation in pediatric patients with combined hamartoma of the retina and the retinal pigment epithelium, with an average follow-up of 36.2 months.

ABSTRACT

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

Methods: This retrospective multicenter study included sixty-two eyes of 59 pediatric patients with CHRRPE 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 PPV or followed conservatively. At baseline and each visit, visual acuity values, optical coherence tomography (OCT) for features and central foveal thickness (CFT), and tumor location were noted. Lesions were called as zone 1, if it involves the macular and peripapillary area, 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. BCVA 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 CFT 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 OCT, subretinal exudate and prominent vascular tortuosity were associated with poor visual acuity.

Conclusions: Vitreoretinal surgery is safe and effective in improving vision and reducing retinal distortion in zone 1 CHRRPE in children.

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

INTRODUCTION

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 CHRRPE 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 (TRD), 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 presence of ERM causing macular distortion and development of TRD, 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, TRD 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 of age. 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}

Herein, 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 pars plana vitrectomy and ERM removal (intervention group). When possible, patients underwent genetic testing for neurofibromatosis, NF-1 and NF-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 done, 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). 4) After limited vitreous base cleaning and peripheral

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retina control, a vitreous tamponade (air, C₃F₈, SF₆, 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 that were able to be measured, best corrected Snellen visual acuity converted to Log MAR equivalent (BCVA) and central foveal thickness (CFT) and prominent ellipsoid zone defects on optical coherence tomography (OCT) were measured at 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). CHRPE lesions were classified based on previous reports.¹⁵ Lesions in zone 1 involved the macular and peripapillary area, whereas lesions in zone 2 were outside the macula and peripapillary area and involved the peripheral retina.

Age at diagnosis of CHRPE, data of fundus findings, tumor location, OCT and imaging features were expressed as means \pm 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 7 years of age and younger received amblyopia treatment in both groups. The age at time of diagnosis, either ≤ 7 years of age or >7 years of age, 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's 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 were 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 shown in **Table 1**. A total of 62 eyes of 59 patients with CHRRPE were enrolled in the 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 (NF-1) and 9 patients had a history of NF-2. Three (5.1%) patients had bilateral involvement, and all of them were diagnosed with NF-1 or NF-2. The main initial symptom was diminution of vision (62.9%), followed by strabismus (19.4%).

Functional Outcomes Assessed by Management

BCVA was measurable in 47 (75.8%) eyes. 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**). BCVA 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 log MAR (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 log MAR [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

OCT information was available in 36 (58.1%) eyes. The mean baseline CFT was $636.4 \pm 327.9 \mu\text{m}$; there was no significant difference in baseline CFTs between intervention ($614.6 \pm 130.7 \mu\text{m}$) and conservative ($643.0 \pm 370.0 \mu\text{m}$) groups. The mean final CFT decreased from 614.6 to $427.3 \pm 174.9 \mu\text{m}$ in the intervention group but increased from 643 to $727.8 \pm 463.4 \mu\text{m}$ in the conservative group ($p=0.001$).

CHRRPE 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. BCVA remained stable at 0.05 ± 0.06 in eyes with zone 2 involvement in the conservative group. BCVA of eyes with zone 1 involvement significantly improved from 1.04 ± 0.34 log MAR (Snellen equivalent, 20/219) at baseline to 0.55 ± 0.40 log MAR (Snellen equivalent, 20/70) at 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**). Additionally, in eyes with zone 1 involvement, the mean CFT decreased from $614.6 \pm 130.7 \mu\text{m}$ to $427.3 \pm 174.9 \mu\text{m}$ in the intervention group, whereas it increased from $709.5 \pm 344.2 \mu\text{m}$ to $791.0 \pm 452.1 \mu\text{m}$ 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 (21.9%) lesions were assessed as having smaller areas, 26 (63.4%) lesions as having the same areas, and 6 (14.6%) lesions as having larger areas. In the intervention group, 7 (36.8%)

lesions were assessed as smaller, 11 (57.9%) the same, and 1 (2.4%) larger. In the conservative group, 2 (9.1%) lesions 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 of age 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 of age 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 log MAR (Snellen equivalent, 20/295) at baseline to 0.85 ± 0.68 log MAR (Snellen equivalent, 20/141) at final in those ≤ 7 years of age and from 0.90 ± 0.54 (Snellen equivalent, 20/158) to 0.73 ± 0.55 log MAR (Snellen equivalent, 20/107) in those > 7 years age (**Figure 4-left**). The mean CFT decreased from 807.2 ± 434.4 μm to 769.1 ± 480.4 μm in children > 7 years of age and decreased from 543.6 ± 146.6 μm to 486.2 ± 121.9 μm in those ≤ 7 years age (**Figure 4-right**). Change in lesion size was similar in patients ≤ 7 and > 7 years of age (**Table 3**).

Eyes with favorable (Snellen $> 20/200$) and unfavorable ($\leq 20/200$) 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 to those with 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 (CI) 3.223–18.671]; $\mathbf{p} < \mathbf{0.001}$);

and between baseline BCVA and visual improvement (OR 2.125 [95% CI 0.406–9.504]; $p= 0.045$)

(Table 5).

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 due to the firm adhesion between the retina and ERM. Iatrogenic retinal tear developed in 2 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 5 eyes, air in 11 eyes, SF₆ in 3 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 between 10 months and 66 years of age 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, whereas one (33%) of the remaining 3 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 (5%) patients who had macular CHRRPE causing distortion or vitreous hemorrhage underwent vitreoretinal surgery and 2 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 8 eyes with CHRRPE had vision loss during 7 years of follow up and 2 eyes that received amblyopia treatment had vision increase. In the conservative group of the present study, an increase in vision was observed in 4 (12.9%) eyes 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 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 (CNVM) 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 log MAR [Snellen equivalent, 20/63] vs. 1.34 ± 1.18 log MAR [Snellen equivalent, 20/302]) compared to those with macular involvement. Similarly, Shields et al.⁹ reported that 36% of the patients with poor vision had macular involvement, compared to 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 the present study, since it is not always possible to distinguish CHRRPE lesions as only having peripapillary or macular involvement; lesions can involve both regions. Additionally, posterior pole lesions are the ones that affect vision more than peripheral lesions. All eyes with final BCVAs of <1 Log MAR ($>20/200$ Snellen) had zone 1 lesions in the present study.

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Lesion characteristics

Previously, clinicians compared lesion characteristics at different locations in order 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 CNVM development were more frequent in peripapillary CHRRPEs, although BCVA was better in patients with peripapillary CHRRPE compared to those with macular CHRRPE. In the present 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 (93%) eyes. Another report of outcomes following PPV in 14 pediatric patients found improved vision in 11 patients¹¹. Other case reports found either an increase or no change in vision following PPV surgery^{14,18}. The present 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 thought to help in improvement of vision which was applied for all children under 8 years of age both in the intervention and the conservative groups.

Lesion size

To the best of 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 exams. Since 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 to 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 as well as 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.

A disclosure / conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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FIGURE LEGENDS

Figure 1: Representative images of a patient with CHRRPE who underwent pars plana vitrectomy 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 OCT image shows the epiretinal membrane and CHRRPE lesion of the macula. **D**, Note the flattening of the macula and intact ellipsoid zone a year after surgery. BCVA improved from 20/200 at baseline to 20/60 at final.

Figure 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 to those monitored conservatively.

Figure 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. BCVA remained at counting fingers level in spite of amblyopia treatment during the follow-up.

Figure 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.

Supplemental Digital Content 1. Video demonstrates a case of CHRRPE in a 6-year-old girl with zone 1 lesion who is treated with PPV and peeling of epiretinal membrane and internal limiting membrane peeling.mov

Table 1. Baseline demographic and clinical characteristics of the patients with CHRRPE

	<i>Intervention Group</i>	<i>Conservative Group</i>	<i>Total</i>	<i>P</i>
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 ^a
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 ^b
Female (n, %)	11 (52.4%)	14 (34.1%)	25 (40.3%)	0.117 ^c
Bilaterality (n, %)	1 (5.0%)	2 (5.1%)	3 (5.1%)	0.964 ^d
Mean baseline BCVA (LogMAR)	1.06±0.41	0.98±0.79	1.01±0.69	0.703 ^a
Snellen equivalent	[20/229]	[20/190]		
Mean baseline CFT (µm)	614.6±130.7	643.0±370.0	636.4±327.9	0.834 ^a
95% CI	[487.1, 804.8]	[495.2, 1048.7]		
Main first sign & symptom				0.402 ^c
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^c
Zone 1	21 (100%)	31 (75.6%)	52 (83.9%)	
Zone 2	-	10 (24.4%)	10 (16.1%)	
Associations				0.324 ^c
NF-1	2 (9.5%)	2 (4.9%)	4 (6.5%)	
NF-2	1 (4.8%)	8 (19.5%)	9 (14.5%)	

Bold values indicate statistical significance. BCVA, best corrected visual acuity; CFT, central foveal thickness; CI, confidence interval; NF, neurofibromatosis.

^aIndependent samples *T* test

^bMann Whitney U test

^cChi-square test

^dFisher's Exact test

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Table 2. Final outcomes of the patients with CHRPE

	Intervention group n:21	Conservative group n:41	<i>P</i>
Eyes with an increase in BCVA*	11 /16 (68.8%)	4/31 (12.9%)	<0.001^a
Eyes with a decrease in BCVA*	1/16 (6.2%)	1/31 (3.2%)	0.570 ^b
Eyes having at least ambulatory vision* (logMAR≤1.7, Snellen ≥20/1000)	14/16 (87.5%)	24/31 (77.4%)	0.436 ^a
Mean final BCVA (LogMAR) Snellen equivalent	0.65±0.55 [20/89]	0.91±0.64 [20/162]	0.232 ^c
Mean final CFT (µm) 95% CI	427.3±174.9 [222.3, 680.1]	727.8±463.4 [513.1, 1068.9]	0.105 ^d
Eyes receiving amblyopia treatment (n, %)	16 (76.2%)	24 (58.5%)	0.281 ^a
Complications			
Rhegmatogenous retinal detachment	1 (4.7%)	-	NA
Hypotonia	1 (4.7%)	-	NA
<p>Bold values indicate statistical significance. BCVA, best corrected visual acuity; CFT, central foveal thickness; CI, confidence interval; NA, not applicable. *Not available in patients of preverbal ages. ^aChi-square test ^bFisher's Exact test ^cMann Whitney <i>U</i> test ^dIndependent samples <i>T</i> test</p>			

Table 3. Baseline characteristics of the patients with CHRRPE according to age

	<i>≤7 years of age</i>	<i>>7 years of age</i>	<i>P</i>
Number of patients (n, %)	36 (61.0%)	23 (38.9%)	
Mean baseline BCVA (Log MAR) (n=47)	1.17±0.71	0.90±0.54	0.130 ^a
Snellen equivalent	[20/295]	[20/158]	
Mean baseline CFT (μm) (n=36)	543.6±146.6	807.2±434.4	0.028^b
Main first symptom			0.020^c
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 ^c
Zone 1	31 (81.6%)	21 (87.5%)	
Zone 2	7 (18.4%)	3 (12.5%)	
Size (n=42 eyes)			0.482 ^c
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. BCVA, best corrected visual acuity; CFT, central foveal thickness.

^aIndependent samples *T* test

^bMann Whitney U test

^cChi-square test

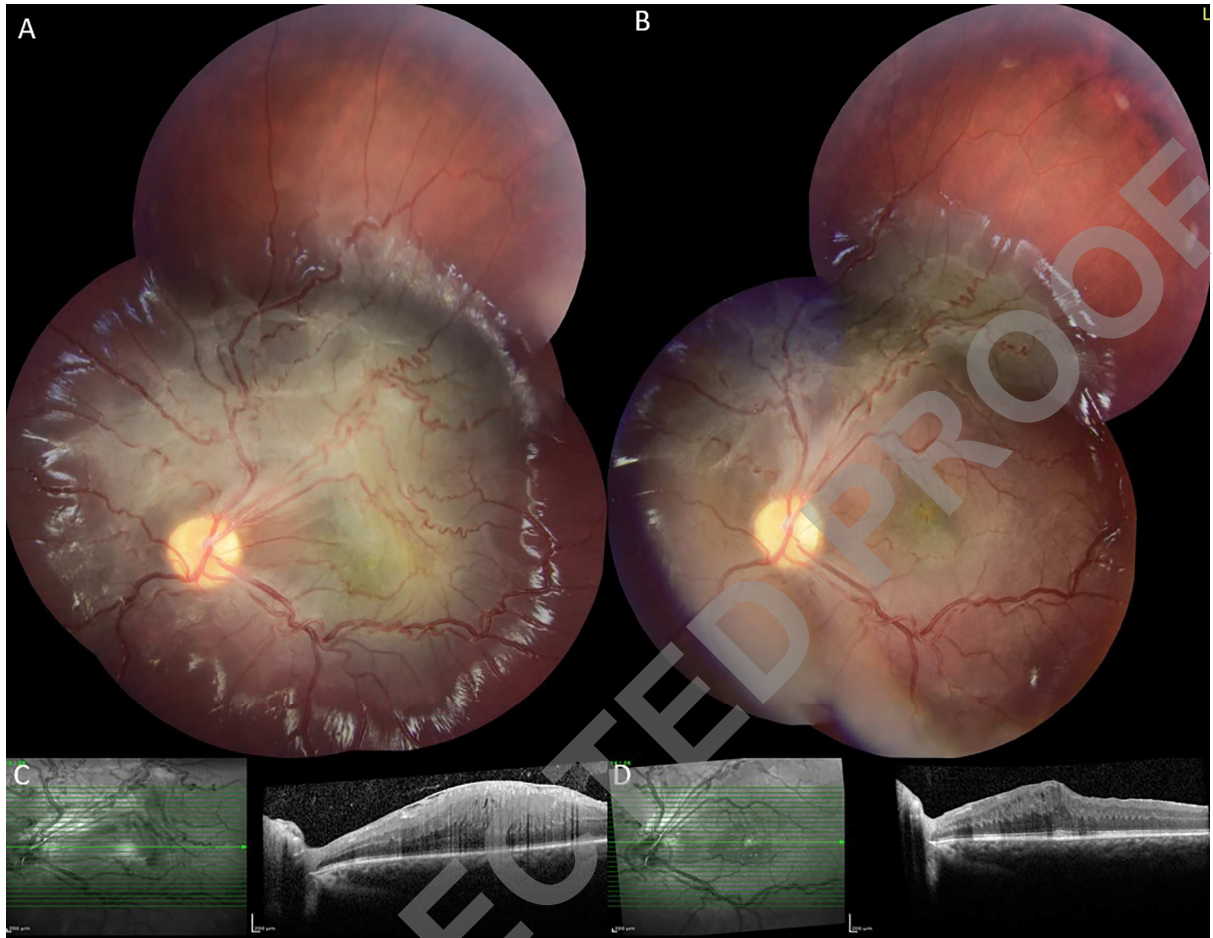
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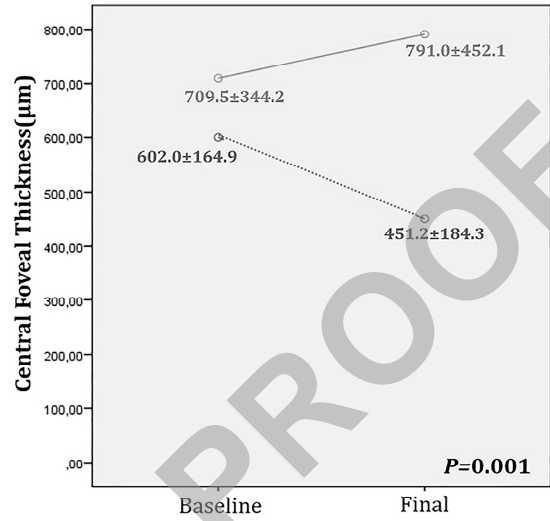
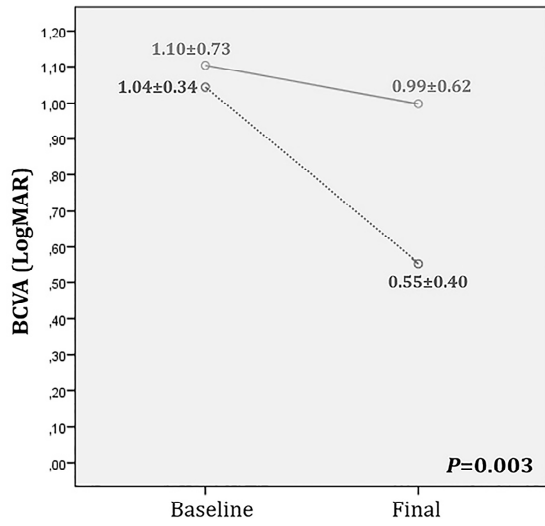
Table 4. CHRPE characteristics of the patients according to final visual outcome				
	Final BCVA >20/200 n:30	Final BCVA ≤20/200 n:17	Total	P
Lesion location				0.050^a
Zone 1	23 (57.5%)	17 (42.5%)	40	
Zone 2	7 (100%)	-	7	
Lesion size with time (n:33)				0.529 ^a
Remained stable	15 (50%)	8 (47.1%)	23 (69.7%)	0.846 ^b
Enlarged	2 (6.7%)	2 (11.7%)	4 (12.1%)	0.547 ^b
Became smaller	5 (16.7%)	1 (5.9%)	6 (18.2%)	0.287 ^b
Fundus findings				0.033^a
Epiretinal membrane	26 (86.7%)	16 (94.1%)	42 (89.4%)	0.426 ^b
Vascular tortuosity	11 (36.7%)	11 (64.7%)	22 (46.8%)	0.044^b
Pigmentary changes	9 (30%)	3 (17.6%)	12 (25.5%)	0.351 ^b
Subretinal exudate	-	5 (29.4%)	5 (10.6%)	0.002^b
Tractional retinal detachment	4 (13.3%)	1 (5.9%)	5 (10.6%)	0.426 ^b
OCT - Fovea (n:36)				0.019^a
Normal	9 (30%)	-	9 (25%)	0.012^b
Flat	1 (3.3%)	2 (11.7%)	3 (8.3%)	0.256 ^b
Bumpy	13 (43.3%)	11 (64.7%)	24 (66.7%)	0.159 ^b
OCT - Ellipsoid zone defect (n:36)				0.018^a
Normal	15 (50%)	3 (17.6%)	18 (38.3%)	0.028^b
Mild	4 (13.3%)	-	4 (8.5%)	0.115 ^b
Moderate	2 (6.7%)	1 (5.9%)	3 (6.4%)	0.916 ^b
Severe	2 (6.7%)	9 (52.9%)	11 (23.4%)	<0.001^b
Bold values indicate statistical significance. OCT, optical coherence tomography; N/A, not applicable. ^a Chi-square test ^b Calculated p values after post hoc analysis of categorical data				

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 >7 years	0.548	0.361	0.052	2.915
Gender (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.

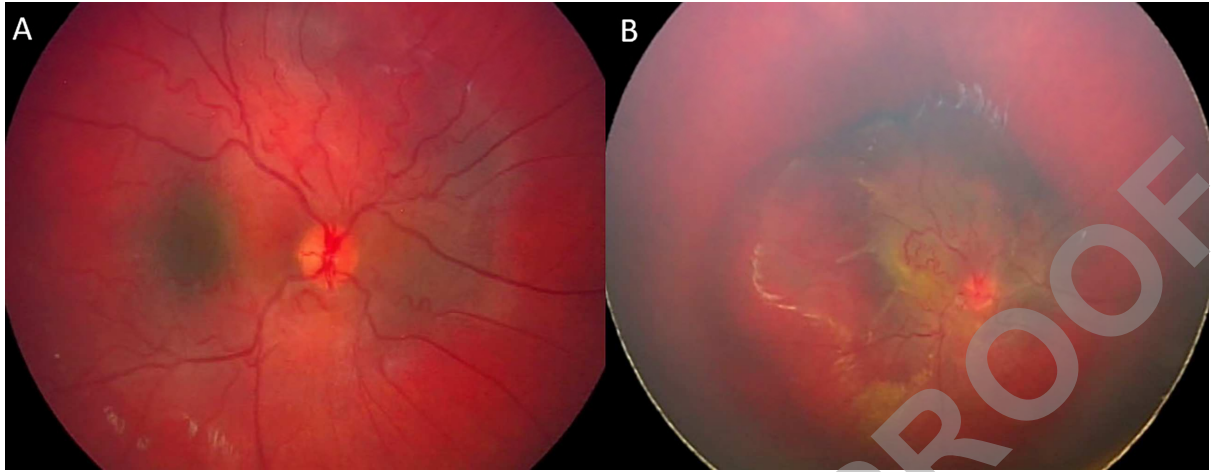


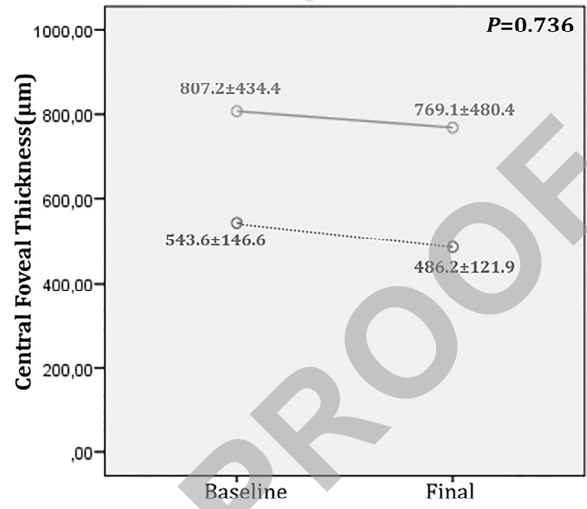
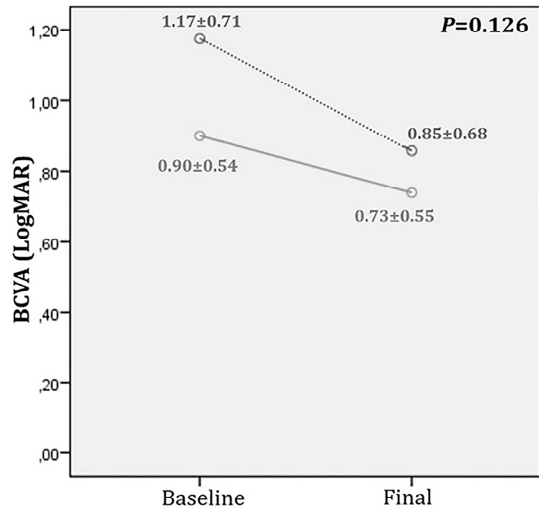


..... Intervention group

— Conservative group

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..... Patients ≤7 years of age — Patients >7 years of age