Advances in Ophthalmology Practice and Research 3 (2023) 9–14

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Review

Description and surgical management of epiretinal membrane due to combined hamartoma of the retina and retinal pigment epithelium

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ARTICLE INFO

Keywords:
Combined hamartoma of the retina and retinal pigment (CHRRPE)
Epiretinal membrane (ERM)
Surgery

ABSTRACT

Purpose: To outline the characteristics of Combined Hamartoma of the Retina and Retinal Pigmentation Epithelium (CHRRPE) and provide a comprehensive overview of surgical management of epiretinal membrane (ERM) caused by CHRRPE.

Main text: CHRRPE is a rare ocular tumor. It clinically mimics other diseases such as retinoblastoma and choroidal melanoma. The present study reviewed the multimodal imaging of CHRRPE, highlighted the multimodal imaging modalities which are useful for revealing the unique features of CHRRPE and hence allowing physicians to confirm the diagnosis.

Although most of CHRRPEs are benign harmatoma, progressive visual loss may occur because of the traction of the tumor and other complications. It is treated through surgical removal of the ERM caused by CHRRPE to free retina from the traction. Currently, there is no consensus on the surgical management of CHRRPE. Therefore, the current review was designed to explore the surgical management of ERM caused by CHRRPE and hence provide updated data on this subject.

Conclusions: Multimodal imaging technologies, especially optical coherence tomography (OCT), significantly contributes to the diagnosis of CHRRPE and visual prognosis. Surgical management of CHRRPE through removal of ERM is beneficial in patients with worsening VA which is secondary to ERM which is associated with CHRRPE. However, the strategy is limited to patients with long-standing poor vision. However, earlier surgical therapy and subsequent postoperative amblyopia therapy can be explored for children of amblyogenic age.

1. Introduction

Combined Hamartoma of the Retina and Retinal Pigment Epithelium (CHRRPE) is a rare benign solitary tumor that is more common in children. The mean diameter and thickness of the lesion are 7.6 and 1.9 mm, respectively. The lesion is usually unilateral. It usually changes little in size over time, unless there is Epiretinal Membrane (ERM) or Choroidal Neovascularization (CNV) progression.[1] Although it is generally not related to other diseases, it has been linked to neurofibromatosis type II, neurofibromatosis type I, Gorlin Goltz syndrome, Poland anomaly, branchio-oculofacial syndrome, and juvenile naso-pharyneal angiofibroma.[2] It is mainly accompanied by symptoms of diminishing Visual Acuity (VA), metamorphopsia or strabismus.[3]

CHRRPE was first coined by Gass in 1973.[4] He summarized the clinical characteristics of CHRRPE: (1) It was a slightly elevated, charcoal grey malformation involving the Retinal Pigment Epithelium (RPE), retina, and overlying vitreous; (2) It presented as a fanlike projection extended into the periphery; (3) Base of the lesion was blended imperceptibly into the surrounding RPE; (4) The inner and central portion of the lesion was covered by thickened grey-white retinal and preretinal tissue; (5) Retinal disruption and vessel displacement were caused by the contraction of the inner surface of the lesion; (6) No atrophic changes in RPE and choroid surrounding the edges of the lesion; (7) The lesion was not associated with retinal detachment (RD), hemorrhage, exudation, and vitreous inflammation (Fig. 1).

Although CHRRPE is most commonly located near the disk, it can also

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https://doi.org/10.1016/j.aopr.2022.09.001
Received 28 May 2022; Received in revised form 7 September 2022; Accepted 16 September 2022
Available online 15 October 2022

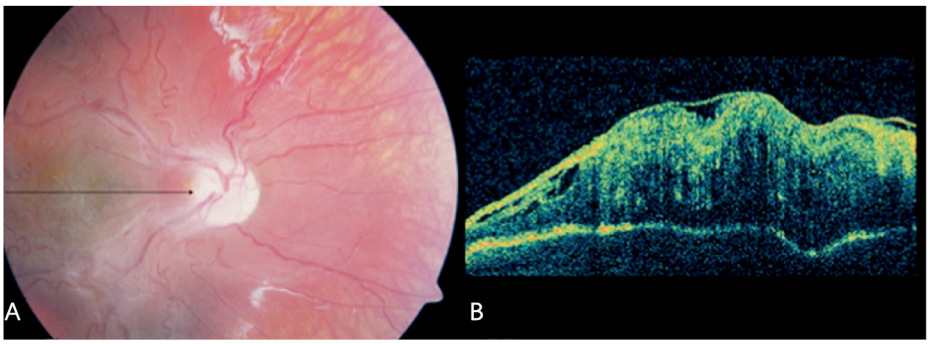

Fig. 1. Fundus and OCT presentation of CHRRPE
CHRRPE with OCT images of full-thickness retinal folds and epiretinal membrane.[2]

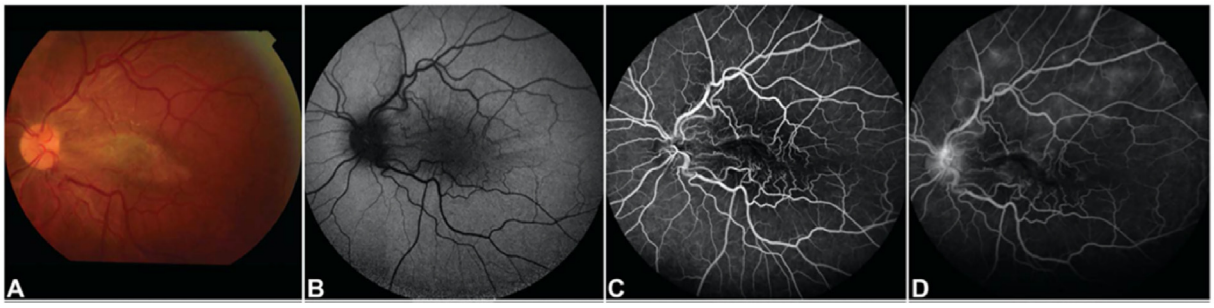

Fig. 2. Fundus and FFA presentation of CHRRPE
CHRRPE with fundus, autofluorescence and FFA images of early hypo-fluorescence (C) caused by obstruction from the CHRRPE, tortuous vessels (B,C, and D), and late dye leakage (D).[17]

be found in the macula or midperiphery.[4] In addition, a study conducted by Gupta et al.[5] found that there is a difference in the severity of retinal disruption between peripapillary and macular combined hamartoma. The amount of pigmentation and retinal distortion was larger in the peripapillary than in the macula lesion.

CHRRPE is histologically constituted of varying proportions of melanocytic, vascular, or glial cells which appear to dominate its clinical presentations.[6] Color variations in the composition of cell types are responsible for heterogeneous clinical manifestations. Therefore, diagnosis of CHRRPE can be confused with other diseases such as choroidal melanoma, and retinal hemangioma, retinoblastoma.[6] Some CHRRPE appear to predominantly containing vascular cells (mostly red cells). Other CHRRPE contain prominent melanocytic cells (mostly black color), and some appear to have a predominance of glial cells (mostly white color). The *trans*-differentiation from glial and RPE cells into myofibroblastic pre-retinal cells alters the vitreoretinal interface, resulting in the formation of an ERM.[6,7] The ERMs are a common feature of CHRRPE. In some cases, it may be difficult to distinguish ERM from CHRRPE. Nevertheless, hyperpigmentation, abnormal vasculature, and young age of the patients are rarely present in ERM as compared with CHRRPE.[8] In most of patients, CHRRPE can be distinguished from retinal astrocytic hamartoma by fundus differences. Retinal astrocytic hamartoma is more likely to present as a yellowish or white translucent plaque, nodule or mulberry-like lesion, with or without calcification.[9,10] In addition, CHRRPE have no distinct feeder vessels supplying the tumor, which can be distinguished from RPE adenoma.[11]

Contraction of ERM caused the secondary formation of radiating retinal folds, local retinal vascular distortion, traction Retinal Detachment (RD), macular retinoschisis, and chronic macular edema in these patients can lead to significant VA reduction and metamorphopsia.[3] Prognosis of ERM is poor without treatment. Further, only one case has been previously reported with spontaneous separation of ERM in CHRRPE.[12]

2. Multimodal imaging evaluation of CHRRPE

More complete comprehension of retinal microarchitecture changes induced by CHRRPE can be found because of the clinical applications of multimodal imaging analysis and developments in imaging methodology over time.

Fluorescein Angiography (FFA) characteristics of CHRRPE (Fig. 2) includes early hypo-fluorescence caused by obstruction from the CHRRPE, tortuous vessels, and late dye leakage.[6]

Moreover, OCT (Optical Coherence Tomography) may delineate ERM with corresponding retinal folds and striae.[13] The first description for CHRRPE on OCT was reported by Ting et al.[14] The CHRRPE exhibited as a thickened mass with hyperreflectivity in the retina and extensive shadowing of the underlying tissue.

A study carried out by Shields et al. examined the spectral domain-OCT (SD-OCT) imaging of 11 patients in 2005.[13] The presence of ERM and inward retinal traction were found in all the examined patients showing a full-thickness retinal disorganization. In the described previous studies, it was evident that involvement of CHRRPE was limited to the inner retina. According to Arepalli et al.,[15] this was because of the technical limitations of SD-OCT, which prevented the deeper structures from being clearly imaged. Mini-peaks (saw-tooth pattern) and maxi peaks (retina folded pattern) were used to describe the vitreoretinal traction on EDI-OCT in the study conducted by Arepalli et al. The mini-peaks generally indicated inner retinal traction and no outer retinal disruption. The maxi-peaks showed full-thickness retinal folds, and superficial as well as deep retinal distortion which was vertically and laterally pulled. Eight cases were included in the study. This study discovered mini-peaks in the inner retina (five eyes), maxi-peaks in the entire thickness retina (six eyes), and a mix of mini- and maxi-peaks (three eyes) due to substantial vitreoretinal tension. Elsewhere, Kumar et al. also found a saw-tooth appearance in the Outer Plexiform Layer (OPL).[8,16] The term “omega sign” was used to describe a deeper and

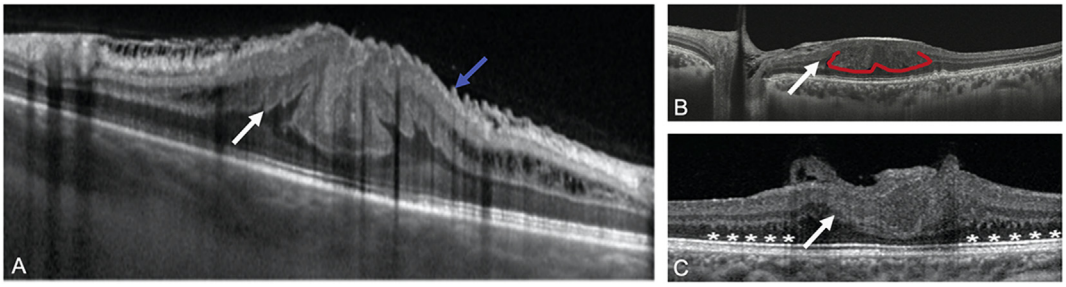

Fig. 3. Example of mini-peaks (blue arrow), maxi-peaks (white arrow)/omega sign (red) and shark teeth appearance (asterisk) with marked retinal distortion
Mini-peaks: inner retinal traction and no outer retinal disruption; maxi-peaks: full-thickness retinal folds; omega sign (red): broader and deeper maxi-peaks that look like omega-shaped; shark teeth appearance (asterisk): triangular hyperreflective alterations that located in the Outer Nuclear Layer (ONL).[15–17]

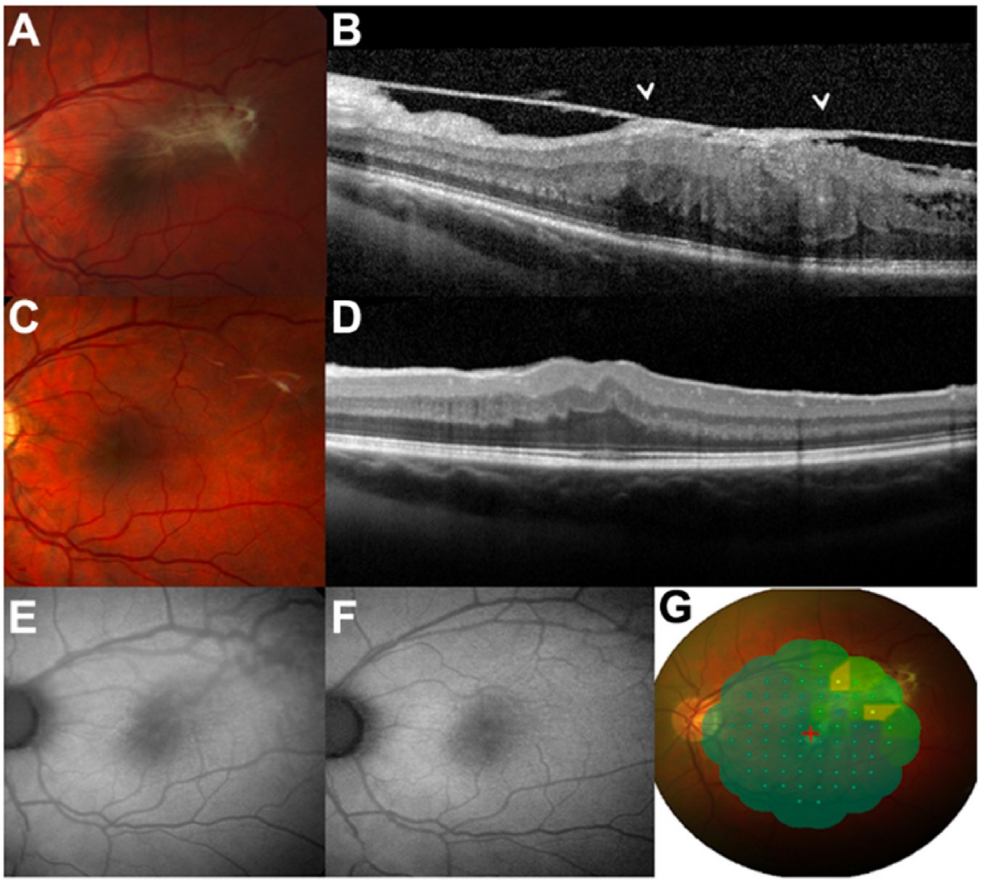

Fig. 4. Fundus (A and C), OCT (B and D), autofluorescence (E and F) and MP-1 (G) presentation of CHRRPE
Image comparison of a patient before surgery (A, B, and E) and post operation (C, D, and F). Lower retinal sensitivity showed by preoperative MP-1 (G) indicated the area with higher adherence of the ERM to CHRRPE.[18]

broader saw-tooth appearance. This sign was caused by the vertical force of OPL from the tumour in the inner retinal layers and the lateral force from the contraction of ERM, both of which were consistent with maxi-peaks. According to Kumar et al., it was suggestive that the "omega sign" can be helpful to distinguish macular CHRRPE from idiopathic ERM. In conclusion, it is evident that the sawtooth pattern can present on the surface of the tumour as a mini-peak and the intraretinal layers as a maxi-peak/omega sign, whereas the omega sign may be more representative.

Recently, Arrigo et al.[17] identified a new feature known as the "shark-teeth" sign (Fig. 3). This was detected on structural OCT which is located in the Outer Nuclear Layer (ONL) and demonstrated as a small triangular hyperreflective alterations.

The combination of MP-1 microperimetry, SD-OCT, and fundus autofluorescence imaging was first used by Brue et al.[18] (Fig. 4). Results of the study showed that a lower sensitivity before the surgical care was associated with a worse VA. MP-1 microperimetry can detect the low sensitivity of the retinal area and hence indicating the adherent ERM. Therefore, the microperimetry can be used as a predictor before surgical intervention.

The Optical Coherence Tomography Angiography (OCTA) can clearly show the anomalies of retinal vasculature induced by ERM and tumour shrinkage in the tumour area[17,19] (Fig. 5). A study conducted by Scupola et al.[20] described the evaluation with OCTA in two cases with CHRRPE. Furthermore, unlike FFA, OCTA is a non-invasive and reliable method that does not require the injection of any dye.[17] However, as previously

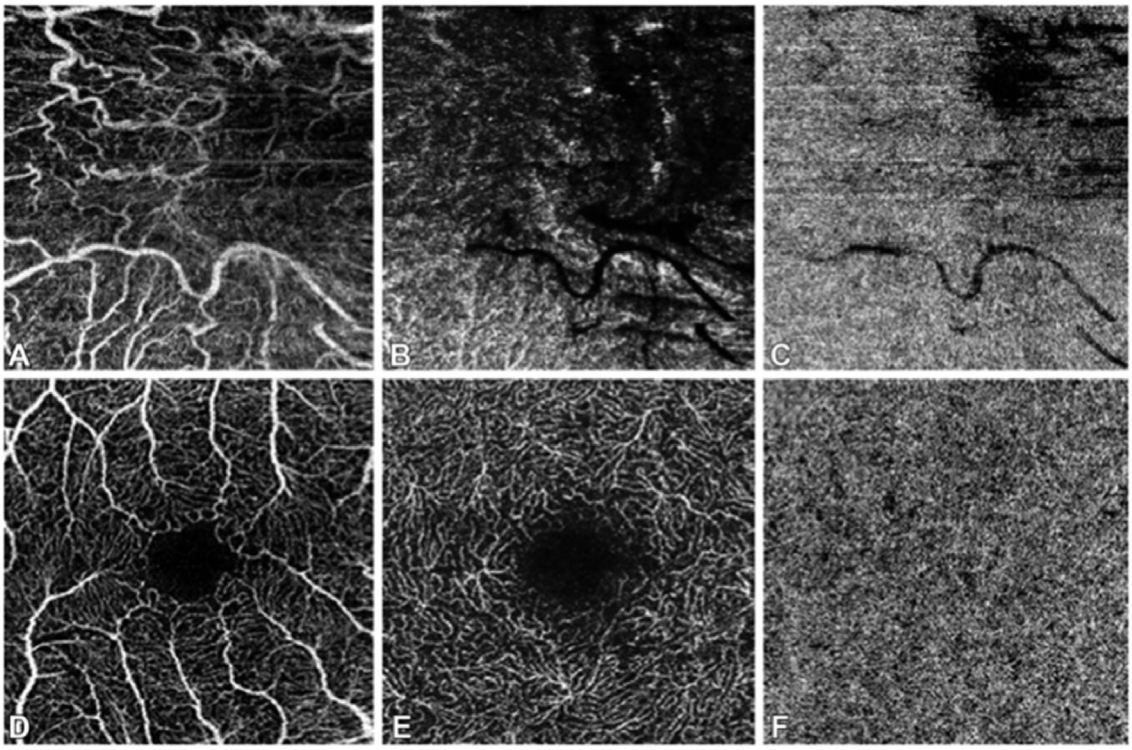

Fig. 5. OCTA presentation of CHRRPE
The superficial (SCP) and deep (DCP) (A and B) capillary plexa and choriocapillaris (CC) (C) of a patient of CHRRPE. Compared with the contralateral eyes, OCTA showed vessel rarefaction, increased vascular distortion, foveal avascular zone loss, and overall disruption of the vascular network in SCP (D), DCP (E), and CC (F).[17]

noted by the authors, there is need for more studies of the CHRRPE on OCTA to highlight the new features of vascular modification in CHRRPE.

In summary, it was evident that the combination of multimodal imaging tools improve diagnosis of CHRRPE. The disruptions of CHRRPE in the inner retina (mini-peaks), the full thickness retinal fold limited to the OPL (maxi-peaks/omega sign), or the small triangular hyperreflective alteration (shark-teeth) in the ONL can be found on OCT (Fig. 3). The vessel tortuosity of CHRRPE can be presented on FFA or OCTA. Therefore, the unique combination of these characteristics makes it easier to distinguish CHRRPE from other disorders.

Furthermore, the surgical management can be carried out with the aid of multimodal imagings for evaluation. For instance, MP-1, can be used as a diagnostic adjunct to identify the traction occurring along with the vitreoretinal interface. Moreover, surgeons can predict the visual outcomes after surgery depending on the degree of retinal disorganization based on the degree of disturbance of the retina on OCT.

3. Surgical management of epiretinal membrane

The aim of surgical treatment is to remove the ERM and free the retina from traction. However, surgical treatment of CHRRPE through removal of ERM still remains controversial. There are few reports or small studies about the results of surgery. According to some academicians, the overlying glial membrane is often interwoven into the dysplastic retina itself and this made it difficult to peel the membrane. Therefore, VA has a limited chance to be improved through surgical management. To address this challenge, a review of the published reports on CHRRPE surgery was analyzed in the current study (Table 1).

A total of 13 small case reports (43 patients) have shown that surgery results shows good visual outcomes (success rate >70%).[17,18,21–31] It was found that 39 of the 43 patients (90.7%) had postoperatively improved in VA. Because of rarity of the disease the largest cohort study was published by Sun et al.[30] in 2020 with only 15 patients.

Indeed, some studies have presented negative results on VA after surgery.[6,32,33] The first surgical outcomes was published in Macular Society's series by Schachat et al.[6] in 1984. The authors reported that 3 out of 60 patients with CHRRPE underwent ERM peeling. It was found that only one patient an improved vision after the surgery. They proposed that the vitreoretinal surgery for ERM peeling should be limited to patients whose membranes do not blend into the lesion. In 1985, McDonald et al.[32] reported two patients with CHRRPE and progressive visual loss despite the surgery. Both patients had preoperative cystoid macular edema and relatively protracted periods of poor vision. However, VA did not improve in either patient after surgery. The negative functional result was attributed to long-term edema or traction, or both, which produced photoreceptors damage. Furthermore, the above two investigations performed PPV in 1984 and 1985, implying that they were relatively old surgical methods and instruments. In a separate study, Zhang et al.[33] attempted to peel the membrane that adhered firmly to the retina in 2009. However, despite the careful peeling that preserved the integrity of the hamartoma, the results were not promising. The VA improved only in three out of five (60%) patients. Elsewhere, Zhang et al. hypothesized that another reason for the negative results could be the lack of timely amblyopia therapy in some pediatric patients.

Recently, there have been some concerns about the outcome of ERM surgery in young children.[34,35] Some scientists postulate that better VA outcomes may be achieved if ERM peeling is performed at an early age, leading to less deterioration of the macular anatomy. However, the posterior vitreous of pediatric patients strongly adhered to the internal limiting membrane, than that of adults.

Several studies have suggested that patients with macular distortion of amblyogenic age can achieve a better VA after surgical treatment and subsequent postoperative amblyopia therapy.[27,29,30] In According to Cohn et al., 2009, it was proposed that the autologous plasmin enzyme may be an effective surgical adjuvant therapy.[27] It can create a cleavage room to facilitate epiretinal removal and assist in removing extensive traction. Notably, 6 out of the 11 pediatric patients (55%) with CHRRPE underwent ERM peeling, and it was found that 8 out of the 11 patients

Table 1
A comparison of published cases with CHRRPE that underwent ERM removal surgery.

Study	Public year	Number of eyes	Location of lesion (complication)	Mean age at surgery (year)	Mean follow-up (month)	Number in macular anatomy improved	Visual improvement after operation number	Comments
Schachat et al.	1984	3	NA residual	NM	NM	NM	1 (33.3%)	Residual membrane
McDonald et al.	1985	2	Macula (macular edema)	35	6	0	0 (0)	macular edema decrease (1)
Sappenfield et al.	1990	1	Macula	27	6	0	1 (subjective improved 100%)	/
Mason et al.	1997	1	Peripapillary (macular hole)	37	4	1	1 (100%)	/
Mason	2002	1	macula	20	3	1	1 (100%)	/
Benhamou et al.	2002	1	macula	7	NM	1	1 (100%)	/
Stallman et al.	2002	1	macula	10	9	1	1 (100%)	/
Konstantinidis et al.	2007	2	50% peripapillary, and 50% macula	13	9	2	2 (100%)	Restoration of the macular microarchitecture was achieved.
Shields et al.	2008	3	Macula	NM	1	NM	NM	/
Cohn et al.	2009	11	73% macular, 27% macula & peripapillary	4.6	15.6	11	8 (72.7%)	Stressed the assistance of autologous plasmin enzyme at surgery.
Zhang et al.	2010	5	60% peripapillary retina, and 40% macula	12.6	NM, (3–60)	5	3 (60%)	/
Brue et al.	2013	6	50% macula, 33.3% peripapillary area and macula, and 16.7% pericentral retina	31	23	6	6 (100%)	Stressed the guideline of SD-OCT, fundus autofluorescence, and MP-1 results.
Vicente et al.	2017	1	Macular area (Hard exudation)	39	15	1	1 (100%)	/
Arrigo et al.	2018	1	Macular area	NM	12	1	1 (100%)	1-year OCTA showed strong reduction of SCP vascular tortuosity, total restoration of DCP and CC, and only partial alterations of the FAZ.
Mammo et al.	2019	1	Peripapillary retina	12	60	1	1 (100%)	Recurrence of ERM at final visit without visual loss.
Sun et al.	2020	15	67% Macula, 7% macula & posterior pole; 13% peripapillary & macula; 13% midperiphery (Neurofibromatosis Type 1 (1); Peripapillary with TRD involving macula (1))	10	68.4	15	14 (93.3%)	/
Sommen et al.	2021	1	Papillomacular area (Subretinal exudation)	26	48	1	1 (100%)	Complete vitrectomy with detection and removal of VCR is recommended for CHRRPE.

CHRRPE: Combined Hamartoma of the Retina and RPE; NM: not mention; ERM: epiretinal membrane; VCR: vitreous cortex remnants; SCP: superficial capillary plexa; DCP: deep capillary plexa; CC: choriocapillaris; FAZ: foveal avascular zone.

(73%) improved in VA. During the follow-up period, four ERMs recurred, but the final VA were improved through timely surgery and postoperative amblyopia therapy. Cohn et al., proposed that plasmin-assisted surgery may be used to treat pediatric CHRRPE with ERM. However, there is still need for a large cohort study to validate the effect of autologous plasmin enzyme on the surgery of CHRRPE.

In addition, there have been significant advancements in vitreoretinal instrumentation, techniques, and adjuvants. Because of the publication of these small case studies, including improved fluidics control, small-gauge instruments, better internal light sources, and the development of new dyes, that surgical outcomes can be improved and complications reduced.[31]

Consequently, application of current vitrectomy in early surgical management of ERM and subsequent amblyopia treatment in pediatric CHRRPEs has been recommended with the better technique of current vitrectomy to maximize visual potential. However, it has been found that the postoperative prognosis for patients with long-standing poor VA, cystoid macular edema, or the membrane intertwining with the tumor may be unfavorable.

4. Further prospects

There is a need to standardize the guidelines of CHRRPE in terms of diagnosis and indications for the ERM peeling surgery. In addition, a randomized controlled study on the ERM peeling surgery should be designed to identify the benefits of new techniques. Furthermore, it has been shown that the variations in the predominant cell subtypes of CHRRPE may affect visual outcomes of the surgery. However, there is need for further investigations to clarify this possibility.

5. Conclusions

Multimodal imaging technology provides important information regarding the diagnosis of CHRRPE and visual outcomes. Surgical therapy with ERM excision should be considered for individuals with deteriorating VA caused by ERM associated with CHRRPE. However, to maximize visual potential, early surgical management of ERM and subsequent postoperative amblyopia therapy for pediatric CHRRPEs is recommended.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki.

Author contributions

The authors confirm contribution to the paper as follows: JP and PZ designed the review; YW and YY collected and selected information and

data of the pubished studies; HX generated figures and tables; XZ wrote the paper. All authors read and approved the final manuscript for publication.

Funding

This study was partially supported by Shanghai Sailing Program (No.20YF1429700), the Clinical Research Plan of SHDC (No. SHDC2020CR5014-002), the National Natural Science Foundation of China (No. 82171069) , and Hospital Funded Clinical Research, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No.21XHDB08).

Declaration of compeing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Thanks to all the peer reviewers for their opinions and suggestions.

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