Subtle Combined Hamartoma of the Retina and Retinal Pigment Epithelium Causing Recurrent Exodeviation

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Keywords
Combined hamartoma of the retina and retinal pigment epithelium · Pediatric ophthalmology · Retinal tumors · Strabismus

Abstract
A 3-year-old girl presented with recurrent exotropia following primary strabismus surgery. Careful fundus examination of the left eye revealed loss of the foveal reflex and presence of a subtle grayish mass with overlying white fluff. Optical coherence tomography through the lesion revealed disorganization of inner and outer retinal layers with accompanying epiretinal gliosis. Together, these findings were suggestive of combined hamartoma of the retina and retinal pigment epithelium (CHRRPE). No syndromic association was found. CHRRPE is a rare retinal tumor that usually presents with visual loss, strabismus, or follows an asymptomatic course. Retinal tumors must be kept in mind whenever loss of foveal reflex occurs concurrently with strabismus.

Introduction
Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE) is a rare benign tumor of the retina. It is presumed to be a congenital lesion arising concomitantly from the glial, vascular, and melanocytic cellular compartments of the retina and retinal pigment epithelium [1–3]. Characteristic presentation is a unilateral, elevated, greyish mass, located...
inside or outside the vascular arcades, with varying degrees of overlying vitreoretinal interface disturbance and retinal traction [1, 2]. Age at diagnosis varies widely, with patients diagnosed as early as 2 weeks of age in experienced tertiary centers and others, usually with asymptomatic tumors, diagnosed in adolescence or adulthood. Patients present most frequently with vision loss (40–50%), strabismus (28–38%), or with no symptoms at all (23%) [1, 4]. Simultaneous decreased vision and strabismus is the mode of presentation in approximately 4% of cases [1]. Depending on location, size, degree of retinal architecture distortion, and severity of vitreoretinal traction, visual prognosis can either be good or extremely poor, with certain eyes becoming legally blind during early childhood [1].

Most patients have no associated systemic disease. However, many syndromic associations of CHRRPE have been documented, the most prevalent being neurofibromatosis type 2 (NF2). Rarer associations with neurofibromatosis type 1, Gorlin-Goltz syndrome, Potter syndrome, Poland anomaly, branchio-otic syndrome, branchio-ocular-facial syndrome, juvenile nasopharyngeal angiofibroma, and orbital fibrosis syndrome have been described [1, 5, 6]. The differential diagnosis of CHRRPE comprises choroidal melanoma, choroidal nevus, retinoblastoma, toxocariasis, astrocytoma, and hemangioma [1]. Here, we will discuss a case of CHRRPE presenting with recurrent exotropia in a young female patient.

**Case Report**

A 3-year-old girl was referred to our institution for further management of recurrent exotropia one and a half years after primary strabismus surgery. Ophthalmological history was notable for a 30-prism diopter divergent strabismus appearing at 15 months of age. On initial consultation, no abnormalities were seen on dilated fundus examination using binocular indirect ophthalmoscopy. Following a 3-month surveillance period showing no spontaneous improvement, bilateral lateral rectus recessions were performed. Primary surgery took place when the child was 18 months old, with an uneventful postoperative course.

At the age of 3 years, the exotropia relapsed. The ophthalmological examination revealed best-corrected visual acuity (BCVA) of 20/20 in the right eye and 20/50 in the left eye using crowded symbols. Cycloplegic refraction showed +0.5 (+0.5 at 112°) in the right eye and +1.00 (+0.5 at 70°) in the left eye. Cover-uncover testing revealed variable-angle left exotropia. Slit-lamp examination was normal in both eyes.

Fundus examination of the right eye was normal (shown in Fig. 1a). Left eye fundus examination showed a subtle elevated greyish lesion in the papillomacular region with loss of the foveal reflex (shown in Fig. 1b). Accompanying epiretinal gliosis was also present (shown in Fig. 1b). No foveal dragging or vascular tortuosity was noted in the left eye. Optical coherence tomography (OCT) of the right eye was normal (shown in Fig. 2a) whereas it revealed retinal thickening mostly of inner retinal layers in the left eye (shown in Fig. 2b). Retinal nerve fiber, ganglion cell, and inner plexiform layers were markedly thickened and showed an associated epilesional gliotic reaction (shown in Fig. 2b, green arrow). Loss of foveal depression was also visible; however, no epiretinal membrane (ERM) was present. Foveal retinal thickness was 218μm OD compared to 500μm OS. Sub-foveal choroidal thickness measured by enhanced-depth imaging OCT was 283μm OD and 224μm OS (shown in Fig. 3a, b). The “shark-teeth” sign was present on OCT sections of the fovea (shown in Fig. 3b, yellow arrow). Marked thickening of the outer nuclear layer was also present on OCT sections near the fovea (shown in Fig. 3b, green arrow). Near-infrared imaging of the right eye was normal (shown in Fig. 4a). Near-infrared imaging of the left eye showed generalized hyporeflectivity of the macular region with oblique linear hyperreflectivity corresponding to the epiretinal gliosis (shown in Fig. 4b). Fundus and OCT findings were suggestive of a unilateral, solitary, foveal CHRRPE.
The child was otherwise in good health and had no dysmorphic features or psychomotor delay. As CHRRPE can be associated with NF2, dermatological examination and brain MRI were performed; both came back normal. Genetic analysis looking for mutations in the NF2 gene was negative.

Amblyopia treatment with full-time patching of the sound eye for 3 weeks improved BCVA from 20/50 to 20/30 in her left eye. Thereafter, she was prescribed optical penalization of her right eye to maintain visual potential in her left eye.

Discussion

This case represents the lighter end of the spectrum of CHRRPE with anatomical distortion being notably mild. However, poor visual acuity, exodeviation, and strabismic amblyopia were direct consequences of its foveal location.

Poor visual function in CHRRPE is mainly secondary to retinal microarchitecture disorganization, retinal thickening, ERM formation, and subsequent vitreomacular traction. Location of the tumor also plays an important role with macular tumors having a much poorer visual prognosis compared to extramacular tumors. In a report by Shields et al. [1], mean Snellen visual acuity at diagnosis was 20/320 versus 20/80 for macular versus extramacular tumors. Other possible vision-threatening features of the disease include retinal folds, cystoid macular edema, intraretinal exudation, subretinal fluid, retinal detachment, macular holes, choroidal or preretinal neovascularization, and vitreous hemorrhage [1–4].

Modern ocular imaging techniques are essential in helping identify CHRRPE. On OCT, various features may hint toward the diagnosis. Universal findings are loss of normal retinal architecture and retinal thickening. Presence of ERM is also very frequent (83–90%) and a prominent feature of the disease [2, 3]. Vitreoretinal traction secondary to ERM formation has been further subcategorized as being either in a sawtooth (mini-peak) or folded (maxi-peak) configuration according to the severity and appearance of surface retinal folds [4]. Another recently described sign of CHRRPE on OCT is the "shark-teeth" sign as reported in 2018 by Arrigo and colleagues [3] in a cohort of 6 patients where 100% of 6 eyes exhibited the finding.
The so-called “shark-teeth” represents excrescences of the outer plexiform layer into the outer nuclear layer and appears as hyperreflective triangular alterations. Fluorescein angiography can be useful for diagnosis of CHRRPE as increased retinal vascular tortuosity, vascular dragging, abnormal vascular morphology at the posterior pole, and subtle leakage of fluorescein dye from capillaries can be present [2, 3]. OCT angiography of the tumor may show increased superficial vascular tortuosity and rarefaction of the superficial capillary plexus, deep capillary plexus, and choriocapillaris in the tumor area [3]. On enhanced-depth imaging OCT, analysis of choroidal thickness below the tumor epicenter may reveal choroidal thinning (mean, 37% thinner) when comparing with a corresponding point in the fellow unaffected eye [4]. Lastly, ultrasonography usually shows no acoustic shadowing or intraslesional calcification in CHRRPE, allowing differential diagnosis with choroidal melanoma and retinoblastoma, respectively [2]. In addition, choroidal melanoma characteristically exhibits low-to-medium internal reflectivity on A-scan ultrasonography.

Although most CHRRPE are isolated findings, thorough research for syndromic associations is necessary as this tumor can be associated with a variety of systemic diagnoses. Of these, the most notorious association is with NF2. NF2 is a rare (prevalence, 1:60,000) autosomal dominant condition characterized by development of central and peripheral nervous

![Image](image-url)
system neoplasms. These benign tumors have varied histology and are classified as schwannomas, meningiomas, or gliomas (ependymomas, astrocytomas). Cerebral MRI to look for bilateral vestibular schwannomas, a hallmark of the disease, is needed to work up potential NF2. However, vestibular schwannomas usually appear in early adulthood, thus lowering the sensitivity of a negative cerebral MRI in childhood. Ocular findings of NF2 comprise CHRRPE, ERMs, and juvenile posterior subcapsular cataracts, the latter constituting a diagnostic criterion [7]. NF2 gene sequencing is also important for the diagnosis of NF2 and is included in the revised Manchester criteria. Identifying the causal mutation can give information on disease prognosis as missense and splice-site mutations entail lower mortality than truncating mutations [7].

No medical treatment for the hamartoma itself can be offered at this point. However, treatment with intravitreal anti-VEGF may be necessary in the occurrence of choroidal neovascularization [8].

Pars plana vitrectomy with ERM peeling has resulted in improvement of anatomical features with subsequent improvement in BCVA. Indeed, surgical removal of ERMs has been shown to relieve contractile stress and normalize retinal architecture. In a series by Bruè and

Fig. 3. a Right macular EDI-OCT – normal. b Left macular EDI-OCT – irregular retinal thickening associated with disorganization of inner and outer retinal layers. Choroidal thickness is 224 μm. Yellow arrow shows “shark-teeth” sign. Green arrow indicates marked thickening of outer nuclear layer.
colleagues studying the effect of pars plana vitrectomy with ERM peeling on visual acuity in 6 eyes with CHRRPE, preoperative BCVA rose from 0.3 ± 0.08 (decimal) to 0.9 ± 0.17 in the postoperative period. However, sometimes BCVA remains unchanged despite good anatomical results. This is mostly due to amblyopia or incomplete removal of ERMs. Especially in younger children, ERM peeling can prove very challenging because of increased adherence between the posterior vitreous and the internal limiting membrane [9, 10].

In summary, this case highlights an unusual cause of strabismus recurrence. Horizontal deviations are known to often recur after surgery, even in patients with no organic issues [11, 12]; however, in this particular case the poor vision in the left eye can explain the recurrence of the strabismus.

In addition, one should keep in mind that fixed exotropia in a young child can be related to various organic and neurological causes (i.e., 3rd nerve palsy, hydrocephalus, craniosynostosis, Prader-Willi syndrome, etc.) [13–16]. Naturally, a thorough ophthalmological evaluation was performed when the child was first evaluated. However, the lesion being particularly discrete, it eluded initial fundus examination. Moreover, CHRRPE can grow over time [17]; it might have been smaller at initial presentation and thus easier to miss.

Loss of normal foveal reflex is a very sensitive marker of foveal pathology and was probably an early sign of retinal pathology in this child. However, ophthalmological examination in children can sometimes prove particularly difficult and subtle findings like these can be missed. When faced with a subtle case of CHRRPE without ERM in children, the main focus of treatment should be directed toward amblyopia management as organic and strabismic amblyopia may coexist.

**Conclusion**

CHRRPE differs in presentation, and a spectrum exists between subtle lesions and obvious ones. Therefore, diagnosis of small CHRRPE can be difficult. However, foveal masses must be kept in mind whenever loss of foveal reflex occurs concurrently with strabismus.
Statement of Ethics

Ethics approval for the case report was given by our local Ethics Committee (Comité d’Éthique de l’Hôpital Universitaire des Enfants Reine Fabiola, reference number 112/21). Written informed consent was obtained from the mother of the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Stéphane Abramowicz, MD, and Philippine Delvaux, MD: writing of the first draft, review, and critique. Martina Maria Delle Fave, MD, Déborah Buisseret, MD, and Lavinia Postolache, MD, PhD: case report project (conception, organization, and execution), review, and critique. Pauline Le Roux, MD: review and critique. Equal contributions made to the article: Stéphane Abramowicz, MD, and Philippine Delvaux, MD.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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