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Non-nasal, atypical retinochoroidal coloboma in pediatric patients: Case series and review

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ABSTRACT

Purpose: To report 2 cases of atypically located, non-nasal colobomas in the pediatric population.
Observations: A 3-week-old female neonate with no known past ocular or medical history was diagnosed with temporal iris and chorioretinal coloboma with tractional membranes upon examination under anesthesia and imaging. A 9-year-old female with a history of bilateral sensorineural hearing loss and left mild hydronephrosis presented with a temporal chorioretinal coloboma associated with retinal detachment.
Conclusions and importance: Very few cases of atypically located, non-nasal pediatric colobomas have been reported, and they lack a clear cause or mechanism of formation. Continued documentation of their occurrence and research into their formation at a molecular and embryological level are warranted to better understand their pathogenesis.

1. Introduction

Ocular colobomas occur in 0.5–2.2 cases per 10,000 live births.[1] They are caused by a lack of or defective closure of the embryonal fissure and typically result in defects in the inferior and inferonasal part of the eye.[2] Colobomas can involve defects in the optic disc, choroid, retina, ciliary body, zonules, and iris.[2,3] Defects range from mild with no impact on visual function to severe, in which cysts form from the margin and extend into the orbit, making visual function obsolete.[2]

Colobomas resulting in defects in other areas of the fundus are termed atypical because they involve areas of the eye that do not originate from the embryonic cleft.[4] After conducting an extensive literature review utilizing PubMed and Google Scholar, we only found two case reports of atypically located, non-nasal colobomas reported in the literature, one associated with persistent fetal vasculature and another associated with posterior embryotoxon.[1,5] We report two unique cases of atypically located, non-nasal colobomas, one associated with iris coloboma and hypoplastic lens and the other with retinal detachment (RD).

2. Findings

2.1. Case 1

A 3-week-old female neonate born full term via normal spontaneous vaginal delivery with no complications and weighing 9 pounds presented to the Bascom Palmer Eye Institute (BPEI) for evaluation of microphthalmos in the right eye (Fig. 1A). Examination in clinic showed microphthalmos, hyperopia with astigmatism ($+13.50 + 8.25 \times 78$) and temporal iris coloboma (Fig. 1B and C) in the right eye and myopia ($-4.75 + 2.5 \times 119$) in the left eye. An exam under anesthesia with multimodal imaging was performed. Intraocular pressure (IOP) was normal bilaterally. Anterior segment exam revealed microcornea (6 mm), temporal iris coloboma involving the pupillary margin, and a hypoplastic lens in the right eye. Cornea size was normal in the left eye (11 mm). Fundus exam showed an anomalous disc with a temporal chorioretinal coloboma affecting the macula and tractional membranes from the optic nerve to the temporal edge of the coloboma superiorly and inferiorly with inferior hemorrhage in the right eye (Fig. 1D). Fundus exam of the left eye was unremarkable (Fig. 1E).

On biometric axial scan, the right and left eyes measured 12.9 mm and 18.9 mm, respectively. B-scan of the right eye confirmed shallow

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tractional membranes, no RD, no retrobulbar cyst, and a small lens. Fluorescein angiography of the right eye showed mild leakage at the edge of the coloboma and peripheral avascularity (Fig. 1F); peripheral avascularity was also found in the left eye (Fig. 1G). These changes were mild, and the decision was made to observe. Intraoperative optical coherence tomography angiography (OCTA) of the right eye revealed thinning of the retina and choroid with disorganization of all retina layers, with no foveal depression. No surgical intervention was indicated at the time.

Concern for inherited retinal disease prompted further investigation with the Inherited Retinal Disorders Genetic Panel by Invitae, (Invitae Corporation, San Francisco, USA; CLIA-certified laboratory). No pathogenic variants were identified. The following variants of unknown significance were identified: heterozygous variant c.619G > A (p.Glu207Lys) in the *ABCA4* gene and heterozygous variant c.5750-2A > G (Splice acceptor) in the *HMCN1* gene. The patient had no known family history of any ocular disease. Magnetic Resonance Imaging (MRI) of the brain and orbits was unremarkable. No further work-up was conducted. The patient and family were instructed on monocular precautions, and the patient continues to follow up with multiple ophthalmic specialists.

2.2. Case 2

A 9-year-old female with a history of bilateral sensorineural hearing loss and left mild hydronephrosis presented to our emergency department complaining of seeing a new onset "black veil" covering her right eye. The patient was born at 36 weeks via elective Cesarean section with no complications. Her parents reported no family history of ocular disease. Examination in clinic showed visual acuity (VA) of 20/125 in the right eye and 20/20 in the left eye and microphthalmos with exotropia in the right eye. Exam under anesthesia revealed microcornea (9.5 mm), a round and normal-appearing iris, and a cataract in the right eye. Cornea size was normal in the left eye (12 mm). Fundus exam showed an inferotemporal chorioretinal coloboma from 6:00 to 9:00 sparing the macula with a macula-off rhegmatogenous RD from 4:00 to 12:00 with no proliferative vitreoretinopathy (Fig. 2A). Further imaging of the coloboma is seen in Fig. 2B. A small retinal break was identified intraoperatively at the edge of the coloboma. The left eye was unremarkable (Fig. 2C).

At this point, a scleral buckle with 23-gauge pars plana lensectomy, vitrectomy, and 1000cs silicone oil was performed on the right eye. Lensectomy was required to improve the surgical view due to the dense

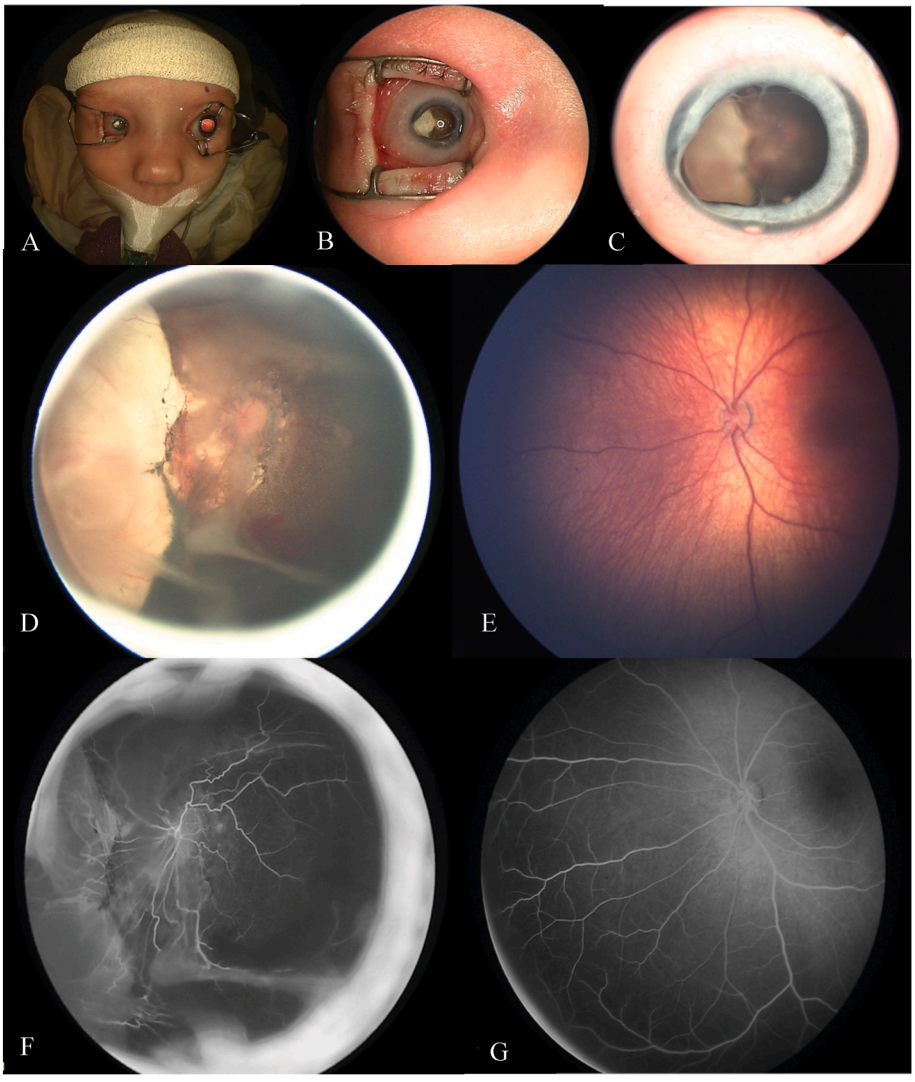

Fig. 1. *Imaging of a 3-week-old patient with a temporal coloboma in the right eye*: (A) Imaging shows microphthalmos of right and left eye. (B) and (C) Imaging shows iris coloboma. (D) Fundus photography shows a temporal chorioretinal coloboma affecting the macula and tractional membranes from the optic nerve to the temporal edge of the coloboma superiorly and inferiorly with inferior hemorrhage in the right eye. (E) No abnormalities in the left eye. (F) Fluorescein Angiography (FA) of the right eye shows mild leakage at the edge of coloboma and peripheral avascularity. (G) FA of the left eye shows peripheral avascularity.

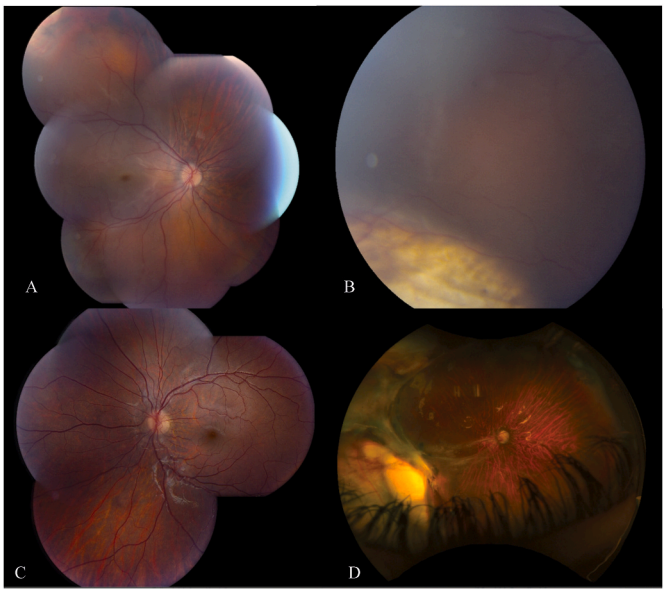

Fig. 2. *Fundus photography of a 9-year-old patient with a temporal coloboma with retinal detachment in the right eye:* (A) Preoperative fundus photograph shows a temporal chorioretinal coloboma with a macula-off rhegmatogenous retinal detachment in the right eye. (B) Preoperative fundus photograph shows a temporal chorioretinal coloboma with associated subretinal fluid in the right eye. (C) No abnormalities in the left eye. (D) Fundus photograph at most recent follow up showing the retina attached under silicone oil.

cataract. Pars plana vitrectomy (PPV) with silicone oil is the most commonly performed procedure associated with RD[6]; combination procedure was chosen to support peripheral pathology and increase chance of surgical success. One year after the surgery, the patient underwent repeat vitrectomy, silicone oil exchange, and membrane peeling for recurrent retinal detachment with proliferative vitreoretinopathy (PVR) and inferotemporal coloboma. Over the next few years, the surgical eye was complicated with secondary glaucoma and required several procedures. At the most recent follow up (8 years after initial presentation), the affected eye has hand-motion visual acuity, controlled IOP and an attached retina (Fig. 2D). Concern for inherited retinal disease prompted further investigation with the Inherited Retinal Disorders Genetic Panel by Invitae, (Invitae Corporation, San Francisco, USA; CLIA-certified laboratory), and no pathogenic variants or variants of unknown significance were identified.

Due to concern for possible syndromic and non-syndromic causes of hearing loss, kidney diseases, and coloboma formation, referral to a clinical geneticist was placed. The patient's mother noted an uncomplicated pregnancy, normal amniocentesis testing, and normal ultrasounds throughout pregnancy. She also noted normal developmental history in the form of achieving speech, gross motor, and language skills at appropriate times and no issues in school. Work-up in the form of karyotype testing, coherence tomography (CT) of temporal bones, electrocardiogram, and echocardiogram, were unremarkable. Genetic testing in the form of *GJB2* gene targeted Sanger sequencing was conducted and revealed no variants (LabCorp, North Carolina, USA; not CLIA-certified laboratory).

3. Discussion

These cases of atypically located, non-nasal colobomas in pediatric patients are unique and have not been previously reported in association with RD.[1,4]

Most colobomas are unilateral but can also be symmetrically or asymmetrically bilateral.[2,7] Fundus colobomas specifically serve as a threat to vision not only due to macula and optic disc involvement, but also due to the substantially increased lifetime risk of RD.[2] Acute onset RD is the most common cause of acute vision loss in a patient with a coloboma, occurring in 23–40% cases.[2,8] Several systemic syndromes and inherited diseases are associated with colobomas. For example, CHARGE syndrome is seen in 15–30% of cases of colobomas.[2] However, specific genetic causes of isolated colobomas remain largely unknown.[9] Even in patients with both a coloboma and microphthalmia, the more common presentation of colobomas, the genetic cause in 20–80% of cases remains unknown depending on severity, bilaterality, and syndromic features.[9] In the second case we report, the patient underwent genetic testing for variants in the *GJB2* gene, which although have been associated with non-syndromic hearing loss,[10] and ocular findings, such as keratitis and neovascularization of the cornea,[10] have not been associated with coloboma formation.

In comparison, sporadic colobomas could be caused by environmental factors that cause insult to the uterus, genetic origin with low penetrance or expressivity, or both.[2] Vitamin A deficiency, maternal diabetes, maternal hypothyroidism, and numerous pharmaceutical agents have been associated with sporadic coloboma formation.[2,11]

Atypical colobomas are speculated to be caused by different processes because they do not originate as a defect of embryonic fissure closure, such as in the case of typical colobomas.[12] At day 22 of embryogenesis, development of the eyes commences.[13] Evagination of the neural tube from bilateral grooves in neuroectoderm forms the optic vesicles.[13] At approximately five weeks, the neuroectodermal outpouchings form and create a depression distally, leading to auto-invagination and the formation of a double wall of neuroectoderm.[13] This wall becomes the optic cup.[13] As the neural tube continues to expand and involute, the interaction of the optic cup and vesicles give rise to the development of the optic fissure.[13] During week seven, the edges of the optic fissure fuse.[13] This process results in the completion of many circumferential structures of the eye.[13] In cases of typical coloboma, this fusion process does not occur.

Mann et al. (1975) initially proposed that intrauterine choroiditis during fetal development was the cause of colobomas in atypical locations.[4] In 1977, Klein et al. demonstrated poor differentiation of the choriocapillaris, outer retina, and retinal pigment epithelium (RPE) on histopathology of an atypical coloboma.[4] They noted an irregular choroidal layer and degeneration of the overlying photoreceptors.[4]

Currently, the pathogenesis of atypical colobomas remains unclear.[14] Leading theories include: (a) defective rotation and poor closure of the fetal fissure due to errors in signaling during morphogenesis[4]; (b) accessory embryonic fissures (as observed in sheep embryos) in atypical locations that fail to close[1]; or (c) poor differentiation of fetal structures.[12] Transgenic mice studies have shown that the presence of RPE is required for normal morphogenesis of the retina and choroid.[4,15,16] Therefore, failure of the RPE to develop can cause poor development of the retina and choroid, appearing as an atypical coloboma.[4]

Other theories include developmental anomalies of the neural crest and ectoderm, such as faulty differentiation and imbalances of growth in parts of the inner and outer layers of the optic cup.[5] Moreover, animal studies have found that optic vesicle cells move in a "pinwheel" fashion with retinal precursors involuting around the rim of the optic cup.[17] Cells that are adjacent early in the process can actually settle in disparate locations in the final optic cup structure; defects in these processes can theoretically form atypical colobomas.[17] Furthermore, one must consider that typical inferonasal colobomas can appear as atypical, temporal colobomas in eyes with severe ocular torsion – although nasalization of vessels at the optic disc should be present as well. Finally, since all major retinal cells are present within the fetus by the fourth month of gestation and all RPE cells are morphologically complete within the first trimester, it is plausible to associate early intrauterine inflammatory processes with coloboma formation as originally proposed by Mann et al. however further evidence is needed.[4]

RD can occur in 8–50% of patients who possess a coloboma,[18] and if it is secondary to retinal breaks outside that area, scleral buckling can be

considered as a treatment option.[19] However, when the coloboma etiology is responsible for RD, different management options are considered,[20] especially because anatomical success rates in surgery of colobomatous eyes range from 40%[21]–100%.[22] Ramezani et al. report that the most prevalent treatment of chorioretinal coloboma associated with RD is pars plana vitrectomy (PPV) and the most commonly used tamponade is silicone oil.[6] Combination procedure was chosen our second case to maximize the chance of surgical success.

4. Conclusions

Atypically located, non-nasal colobomas are rare forms of atypical colobomas that lack a clear cause or mechanism of formation. Continued reporting and research investigating their formation at a molecular and embryological level are warranted to better understand their pathogenesis and guide treatment.

5. Patient consent

Written consent to publish this case series has not been obtained. This case series does not contain any personal identifying information. IRB approval waived.

Disclosures and conflicts of interest

Serena Shah, Natasha Ferreira Santos da Cruz, Patrick Staropoli, Francisco Lopez-Font, and Ta Chen Peter Chang have no conflicts of interest to disclosure. Audina Berrocal is a consultant for Alcon, Allergan, Zeiss, Dutch Ophthalmic Research Center, Novartis, ProQR, and Oculus.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship and agree to the order of authorship presented on title page.

Claims of priority

After conducting an extensive literature review utilizing PubMed and Google Scholar, we only found two case reports of atypically located, non-nasal colobomas reported in the literature, one associated with persistent fetal vasculature and another associated with posterior embryotoxon.

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CRediT authorship contribution statement

Serena Shah: Data curation, Methodology, Resources, Validation, Writing – original draft. **Natasha Ferreira Santos da Cruz:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft. **Patrick Staropoli:** Methodology, Supervision, Writing – review & editing. **Francisco Lopez-Font:** Investigation, Methodology, Writing – review & editing. **Ta Chen Peter Chang:** Methodology, Supervision, Writing – review & editing. **Audina Berrocal:** Conceptualization, Formal analysis, Project administration, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

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