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COL2A1 Mutation Causing Pediatric Macular Chorioretinal Atrophy Associated With Stickler Syndrome

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Abstract

Purpose: To report a case of macular chorioretinal atrophy associated with Stickler syndrome in a pediatric patient with a genetically confirmed *COL2A1* mutation. **Methods:** A single case was evaluated. **Results:** A 3-year-old girl was found to have macular chorioretinal atrophy in the right eye and a retinal detachment in the left eye. Optical coherence tomography (OCT) showed macular chorioretinal atrophy and retinal thinning in the right eye. **Conclusions:** Macular chorioretinal atrophy can occur in Stickler syndrome. OCT imaging can be an important tool to characterize and differentiate these lesions from infectious or degenerative processes. These macular findings in collagen disorders can affect vision, making disease identification essential for early diagnosis and management.

Keywords

Stickler syndrome, macular chorioretinal atrophy, optical coherence tomography angiography

Introduction

Stickler syndrome, historically referred to as hereditary arthro-ophthalmopathy, is an inherited connective tissue disorder caused by mutations in collagen genes and resulting in different disease subtypes.[1] Type 1 Stickler syndrome occurs as a result of mutations in the *COL2A1* gene, accounts for most cases, and is inherited in an autosomal dominant pattern.[1,2] Type 2 Stickler syndrome is characterized by mutations in the *COL11A1* gene, and type 3 Stickler syndrome results from mutations in the *COL11A2* gene[2]; both types result in faulty type XI collagen production.[2] Last, type 4 occurs as a result of mutations in the *COL9A1* or *COL9A2* gene, which cause the formation of defective type IX collagen.[2] In addition, an ocular-only type that lacks systemic manifestations is also caused by mutations in the *COL2A1* gene.[2]

Overall, Stickler syndrome is associated with irregular fibrillar collagen that results in abnormal embryological vitreous development and different vitreous phenotypes.[2] In patients with *COL2A1*, *COL11A1*, and *COL11A2* mutations, Stickler syndrome may be associated with deafness, cleft palate, Pierre-Robin sequence, joint hypermobility, and premature arthritis.[2–4]

In addition to abnormal development of the vitreous, the ocular manifestations of Stickler syndrome include congenital cataract, myopia, lamellar cortical opacities, and anterior segment dysgenesis, which can lead to glaucoma.[2,3,5,6] There have also been reports of megalophthalmos and radial perivascular lattice degeneration.[2] Finally, there is a well-described, high risk for retinal detachment (RD) in patients with some types of Stickler syndrome.[7] Specifically, approximately 60% to 70% of patients with *COL2A1* mutations will experience an RD and of those, approximately 50% will have bilateral RDs.[2,8–10] The risk for RD in patients with *COL11A1* mutations has been reported to be approximately 40%.[11]

We report a unique case of macular chorioretinal atrophy associated with Stickler syndrome in a pediatric patient with a genetically confirmed *COL2A1* mutation. Evaluation was performed with optical coherence tomography (OCT) and OCT angiography (OCTA).

Case Report

A 3-year-old girl with a medical history of megalocornea, alternating esotropia, astigmatism, and high myopia in both eyes presented to a pediatric ophthalmologist with concerns for esotropia of the left eye. The refraction was −16.00 +0.75×160 OD and

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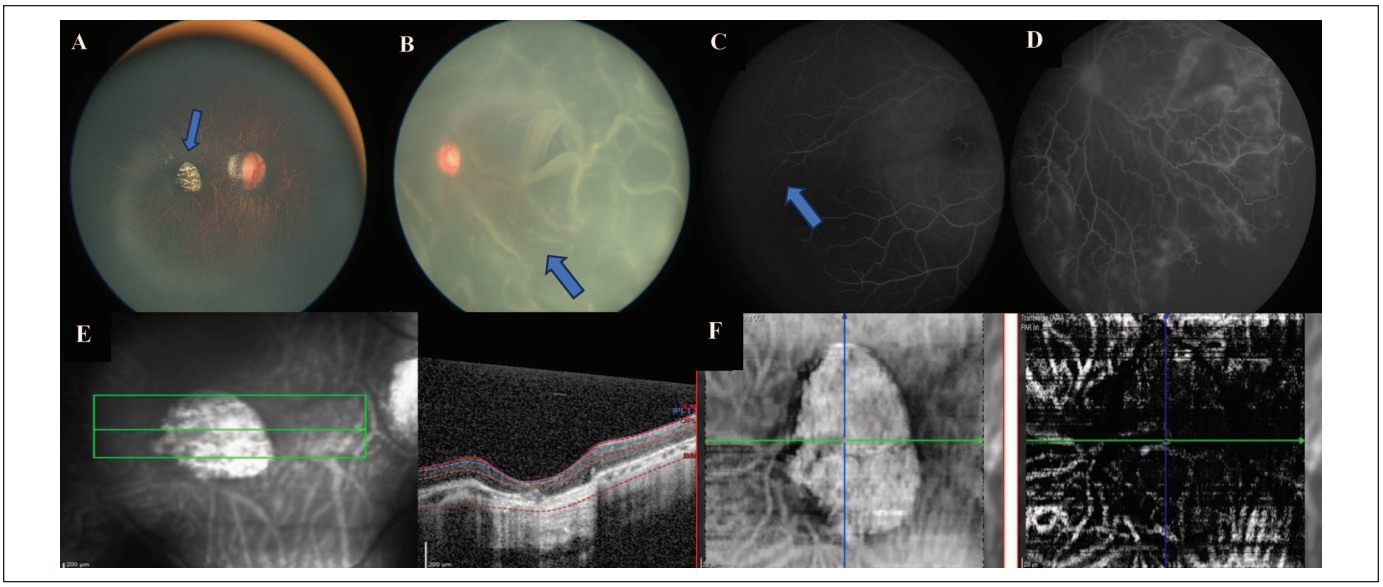

Figure 1. (A) Fundus photography shows a tilted disc, a 1.5 disc diameter area of macular chorioretinal atrophy (blue arrow), a peripapillary scar, attenuated vessels, tessellated fundus, peripapillary atrophy, peripheral avascularity and loss of tessellation, and an attached retina in the right eye. (B) Fundus photography shows a retinal detachment (RD), a break just outside the inferotemporal arcade (blue arrow), and retinal cysts inferiorly in the left eye. (C) Fluorescein angiography (FA) shows 360 degrees of peripheral avascularity with minimal small-vessel leakage (blue arrow) and a central and peripapillary scar in the right eye. (D) FA shows 360 degrees of peripheral avascularity with small-vessel leakage and an RD in the left eye. (E and F) Optical coherence tomography angiography of the right eye shows a circumscribed area of retinochoroidal atrophy with complete loss of choroidal vessels and a small subretinal collection of variably hyperreflective material with choroidal segmentation.

−15.75 +0.75×160 OS. The patient had no family history of Stickler syndrome, high myopia, or RD. The visual acuity (VA), obtained using HOTV optotypes (single pictures), was 20/50 OD. The VA in the left eye could not be determined because of poor patient cooperation.

An examination under anesthesia with multimodal imaging was performed. The intraocular pressure was 13 mm Hg OD and 17 mm Hg OS. The axial length (AL) was 30.7 mm and 27.45 mm, respectively, abnormally long for the patient's age[12]; the asymmetry of the ALs was the result of the RD. A fundus examination of the right eye showed a tilted disc, a 1.5 disc diameter area of macular chorioretinal atrophy, a peripapillary scar, attenuated vessels, a tessellated fundus, peripapillary atrophy, peripheral avascularity, and an attached retina (Figure 1A). The fundus examination of the left eye showed a total RD, a break just outside the inferotemporal arcade, a temporal giant retinal tear, rolled edges, and retinal cysts inferiorly (Figure 1B).

Fluorescein angiography showed 360 degrees of peripheral avascularity with small-vessel leakage in both eyes, a central and peripapillary scar in the right eye (Figure 1C), and a total RD in the left eye (Figure 1D). Intraoperative OCT showed a circumscribed area of retinochoroidal atrophy and retinal thinning in the right eye. OCTA showed that this area in the right eye had a complete loss of choroidal vessels and a small subretinal collection of variably hyperreflective material on the choroid segmentation image (Figure 1, E and F). At this point, combined scleral buckling and pars plana vitrectomy (PPV) with silicone oil (SO) tamponade was performed in the left eye.

An inherited vitreoretinal disorder was suspected; thus, genetic testing was performed with an Invitae Inherited Retinal Disease panel (Invitae Corp; Clinical Laboratory Improvement Amendments–certified). A pathogenic heterozygous mutation was found in the *COL2A1* gene, c.1693C>T (p.Arg565Cys), which is known to cause autosomal dominant Stickler syndrome.

The patient was pseudophakic at the last follow-up visit, with SO tamponade in the left eye. Prophylactic treatment with laser photocoagulation was performed in the right eye. The final VA was 20/300 OD and light perception OS. To date, the retina in the right eye has remained attached. The patient was given monocular precautions and continues to be followed by a pediatric ophthalmologist and a retina specialist.

Conclusions

Certain ocular findings have been described in patients with the c.1693C>T (p.Arg565Cys) mutation in *COL2A1*, as seen in our patient. Richards et al[13] reported various vitreous phenotypes in patients with this mutation, including type 1 congenital membranous vitreous anomaly, which is the most common and is characterized by persistent vestigial vitreous gel in the retrolental space bordered by a folded membrane,[14] in addition to afibrillar vitreous gel without normal lamella structure, which is vitreous gel that forms but is optically empty.[13] Sun et al[15] described a 7-year-old girl with stable high myopia (−16.50 D OD and −14.50 D OS) and no known signs of documented chorioretinal atrophy, unlike our patient. Tian et al[16] found progressive high myopia in an

8-year-old patient without documented chorioretinal atrophy, also unlike our patient. A case series by Huang et al[17] described 3 patients aged 6 years, 8 years, and 10 years who developed bilateral RD during early childhood. One patient had a timely PPV with resultant retinal attachment; however, the other 2 patients developed phthisis in 1 eye. Liu et al[18] reported a 7-year-old patient with a rhegmatogenous RD and multiple peripheral macrocysts.

Macular chorioretinal atrophy has been previously described in the context of a c.1693C>T (p.Arg565Cys) mutation in *COL2A1*. Asano et al[19] documented foveal hypoplasia in 2 families with the p.Arg565Cys mutation in Stickler syndrome, observing an absent foveal pit and macular degeneration, described as the destruction of the outer retinal layers in the macular area. Two patients in the series had been followed since birth, and the degenerative macular changes were first noted at approximately 7 years of age. The authors point out that high myopia could have also contributed to the appearance of the fundus. However, the degenerative changes were not consistently present, even in patients with longer ALs, suggesting an underlying genetic component.

Collagen is a structural protein found in many tissues, including the vitreous and Bruch membrane. It has a notable triple-helix structure comprising 3 polypeptide strands.[20] Although glycine substitutions are usually the cause of triple-helix disruption in some collagen disorders, less common mutations that substitute arginine with cysteine in *COL2A1* can also affect the collagen's triple-helix structure, stability, and secretion, such as in our patient.[21] Specifically, these arginine to cysteine substitutions allow the formation of dimer and trimer collagen proteins linked by abnormal disulfide bonds that are released by the endoplasmic reticulum in small quantities or not released at all, leading to additional abnormalities.[19,22,23]

The mRNA of some type II collagens, such as the product of *COL2A1*, has been documented to be expressed in developmental tissues, including the notochord, heart, brain, and eye.[24] In addition, studies have found that collagens play a role in the assembly, maintenance, structural integrity, and cellular binding properties of various basement membranes.[25] *COL2A1* specifically encodes the alpha 3 chain that makes up type XI and type V collagen.[26–28] Type V collagen comprises a small component of the Bruch membrane. Because *COL2A1* is known to be expressed in the developing eye, it is possible that a mutated *COL2A1* fails to encode the proper alpha 3 chains, resulting in faulty type V collagen, a malformed vitreous and Bruch membrane structure, and possible chorioretinal atrophy.[29,30] That chorioretinal atrophy is not seen more frequently in *COL2A1* mutations could be because type V is not the predominant type of collagen in the Bruch membrane and is variably expressed.

Macular changes can also be a manifestation of other collagen mutations, such as Knobloch syndrome, an inherited collagen disorder with ocular manifestations stemming from mutations in *COL18A1*.[31] Studies have shown an association between the presence of high myopia, macular atrophy, staphyloma, and pseudocoloboma and vision impairment in these patients.[31] Because type XVIII collagen is found in the Bruch membrane, faulty collagen resulting from mutated *COL18A1* is thought to be the mechanism behind the macular atrophy seen in these patients, despite the coexistence of high myopia.[32] A similar mechanism was seen in our patient's case, which makes our theory plausible.

OCTA findings in Stickler syndrome have rarely been reported; however, a study by Navarrete et al[33] found no abnormal vascularization on OCTA imaging in a 9-year-old girl with Stickler syndrome. Eldaly et al[34] reported OCTA findings that included a smaller foveal avascular zone (FAZ) in all eyes (0 to 0.19 mm^2) than in normal eyes and an absent FAZ in 76% of eyes. Matsushita et al[35] found an abnormal pattern of retinal vessels in the posterior poles in eyes with shallow foveal pits. Patterns of upper vessels and lower vessels were seen as highly asymmetric, with the larger vessels running horizontally or obliquely across the capillaries near the fovea and vessels that were abnormally tortuous.

Other retinal conditions known to have manifestations of retinochoroidal atrophy that have been evaluated with OCTA include commotio retinae and geographic atrophy (GA). Utine[36] used OCTA for the evaluation of commotio retinae; the images showed damage to the outer layers of the retina and choriocapillary plexus. Other reports showed that OCTA can be reliably used in the assessment of GA in patients with age-related macular degeneration (AMD) in which the fovea is spared and in patients with AMD in which the fovea is not spared.[37,38] Our OCTA findings of a circumscribed area of retinochoroidal atrophy with complete loss of choroidal vessels and a small subretinal collection of variably hyperreflective material are therefore unique.

Our study comprised only a single case. Moving forward, additional cases of chorioretinal atrophy in the setting of Stickler syndrome caused by the c.1693C>T (p.Arg565Cys) mutation in *COL2A1* would support the association between the mutation and the syndrome. In addition, one must consider that Stickler syndrome is also associated with a significantly longer AL than that in patients with isolated high myopia.[39] This can independently cause varying degrees of macular atrophy and choroidal thinning, with patients presenting with a somewhat overlapping phenotype.[40]

Overall, pediatric patients with genetically confirmed Stickler syndrome can present with macular chorioretinal atrophy at a young age. Macular findings in collagen disorders such as Stickler syndrome can significantly affect vision. Thus, early identification and prophylactic treatment are essential. Furthermore, the use of OCT and OCTA can lead to an early diagnosis that can be confirmed with genetic testing.

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Ethical Approval

The University of Miami Institutional Review Board waived ethical approval of this case report because of the use of de-identified patient data. The case report adhered to the tenets of the Declaration of Helsinki.

Statement of Informed Consent

Written consent to publish this case report was not sought for the present study due to use of de-identified patient data.

Declaration of Conflicting Interest

Dr. Berrocal is a consultant to Alcon, Allergan, Dutch Ophthalmic Research Center, Novartis, Oculus, ProQR, and Zeiss. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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