there is only one other case of *C. trachomatis* presenting as conjunctivitis and preseptal cellulitis.[4] In that case, as in ours, it cannot be definitively stated whether the periorbital changes were reactive[3] to the conjunctivitis or were caused by a secondary bacterial soft-tissue infection. However, the persistence of the periorbital symptoms after administration of non-chlamydia-covering antibiotics, and their complete resolution after azithromycin, suggests that chlamydia was in fact causative of the cellulitis.

Chronic conjunctivitis in children is frequently misdiagnosed as viral in etiology.[5] The ophthalmologist and the pediatrician should maintain a high index of suspicion of chlamydial infection in cases of chronic conjunctivitis, which, if confirmed in a child incapable of consenting to sexual activity, raises the suspicion of child abuse.

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COL4A1 mutations in two infants with congenital cataracts and porencephaly: an ophthalmologic perspective

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***COL4A1* mutations present with a spectrum of clinical phenotypes often involving the cerebrovascular and ophthalmic systems. We report 2 cases of *COL4A1* mutations that presented with congenital cataracts and porencephaly. Both patients had posterior cortical cataracts and radiographically defined bilateral posterior lenticonus. Considering the long-term clinical implications of these mutations, posterior cortical cataracts, bilateral posterior lenticonus, and porencephaly should raise clinical suspicion for *COL4A1* mutations.**

Type IV collagen is a physiologically important component of basement membranes in blood vessels of the brain, eye, kidneys, and muscle.[1] The α1 chain of the *COL4A1* gene contains many highly conserved Gly residue repeats (Gly-X-Y) that are essential to the triple helix structure. Any mutation that leads to the replacement of a Gly residue with a bulkier residue weakens the structural integrity of the triple helix and alters the function of the entire collagen strand.[2] *COL4A1* mutations are associated with a wide spectrum of clinical phenotypes, including intracerebral hemorrhage, porencephaly, cerebral calcification, and hereditary angiopathy, nephropathy, aneurysms, muscle cramping syndrome.[2-5] Congenital cataracts are frequent in patients with *COL4A1* mutations, present in 35 of 157 (22%) patients in one review.[2] In the ophthalmic literature, cataracts and associated eye findings in *COL4A1* patients have not been described in detail. To better characterize the ophthalmic phenotype, we present 2 cases referred to University of Colorado School of Medicine for evaluation.

Case 1

A 9-month-old boy was referred for an absent red reflex and exotropia. After a normal pregnancy, he was born full term without complications. After receiving no early pediatric care, he presented at age 8 months to a pediatrician with right-sided weakness. Family history was negative for ophthalmic problems, stroke, and kidney disease. Physical examination demonstrated right-sided spastic hemiparesis. Magnetic resonance imaging (MRI) of the brain revealed left frontal porencephaly and dysmorphic lenses (Figures 1B and 2A-B). On ophthalmological examination, he exhibited left-eye preference. Slit-lamp examination revealed bilateral central and posteriorly located opacities: 4 mm in the right lens and a <1 mm focal opacity in the left lens. He had a right exotropia of 35$^{\Delta}$, normal pupils, and a normal-appearing fundus. Cataract workup, including testing for TORCH (toxoplasmosis–other agents–rubella–cytomegalovirus–herpes simplex) infections, was negative. *COL4A1* and *COL4A2* genes were sequenced, revealing a c.2969G>T (p.Gly990Val) mutation in the *COL4A1* gene.

The Gly990 residue is completely conserved across species. The missense variant was evaluated by in silico

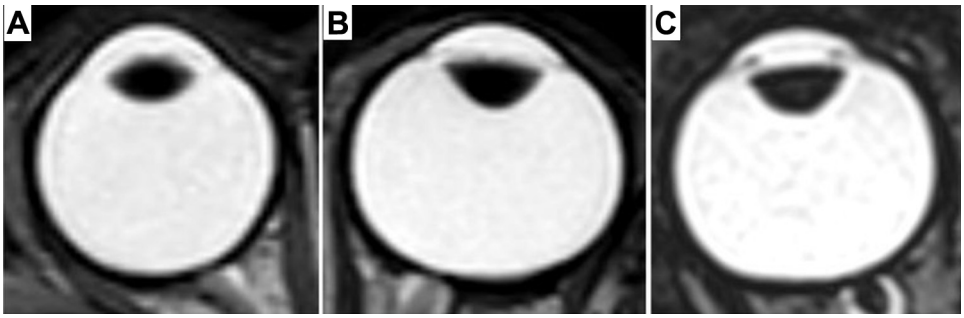

FIG 1. Axial T2-weighted magnetic resonance imaging (MRI) of control and case lenses showing a normal lens (A), a lens with posterior lenticonus in patient 1 (B), and a lens with posterior lenticonus in patient 2 (C).

prediction programs: Polyphen2 showed a pathogenic score of 1.0 (scoring, 0-1) and MutationTaster scored it as disease-causing. The missense variant was previously reported in a 50-year-old man with a history of congenital cataracts and glaucoma presenting with small-vessel cerebrovascular disease following trauma.[6] The parents declined further genetic testing. Given the conservation of the affected amino acid, the results of in silico analyses, the presence in a previously reported patient, and symptoms consistent with previously reported *COL4A1* mutations, we conclude that this missense variant is a pathogenic mutation.[2,5] The patient underwent a cataract extraction and anterior vitrectomy of the right eye and is being treated for amblyopia.

Case 2

A 4-month-old girl was referred for visual delays in the context of developmental delay. She was born full term without complication. Family history was negative for ophthalmic problems, stroke, or kidney disease. Physical examination revealed spasticity, hyperreflexia, and hypotonia. On ophthalmological examination, the patient was not able to follow and had roving eye movements. She had visually nonsignificant 1 mm posterior opacities in both lenses. Pupil and fundus examinations were normal. Brain MRI revealed dysmorphic lenses, enlarged dysmorphic ventricles, and porencephaly (Figures 1C, 2C-D). The MRI demonstrated T1-weighted hyperintensity along the lateral ventricle margins, indicating remote blood products and gliosis. Based on MRI findings and the absence of an ocular cause for visual impairment, she was determined to have cortical visual impairment. Cataract workup, including testing for TORCH infections, was negative. *COL4A1* and *COL4A2* genes were sequenced, revealing a de novo heterozygous c.3190G>A (p.Gly1064Ser) mutation in the *COL4A1* gene. The Gly1064 is completely conserved across species. Evaluation of the missense variant by in silico prediction software returned for Polyphen2 a score of 1.0 (scoring, 0-1), and MutationTaster suggested disease causing. This missense variant has not been previously reported, and the family declined further genetic testing. Given the conserved nature of the affected amino acid, the results of in silico analyses and symptoms consistent with previously reported *COL4A1* mutations, we believe this missense variant is a pathogenic mutation.[2,5] Her cataracts have become increasingly dense with time, although they are not visually significant at 2 years of age.

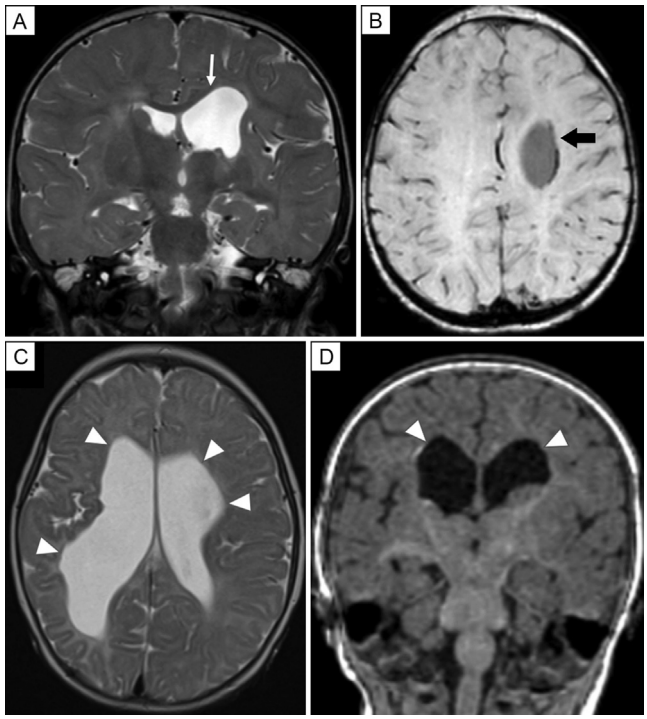

FIG 2. Brain MRI for case 1 and 2. Coronal (A) and axial (B) T2-weighted images of case 1 showing left frontal periventricular porencephaly (white arrow) and hemosiderin staining along the superior margin of the porencephalic cyst (black arrow). Axial (C) and coronal (D) T2-weighted images of case 2 each showing dysmorphic lateral ventricles due to areas of periventricular porencephaly.

Discussion

We present 2 cases with a heterozygous pathogenic mutation in the *COL4A1* gene, who presented with ophthalmic

findings. Both patients had posterior cortical cataracts varying in size from <1 mm to 4 mm. Only one of the 4 eyes had a large enough cataract to be considered amblyogenic. On MRI, all 4 lenses had a posterior lenticonus morphology (Figure 1B-C), which is visually distinguishable from a normal 4-month-old lens on a T2-weighted MRI (Figure 1A).

Posterior lenticonus is a rare finding that is known to contribute to cataract development.[7] Bilateral posterior lenticonus has been reported in association with Down syndrome, Alport syndrome, Lowe syndrome, in addition to biallelic mutations in *FYCO1*.[8,9] Posterior lenticonus is theorized to develop secondary to thinning and weakening of the posterior capsule.[10] Both capsule thinning and lenticonus (typically anterior lenticonus) are well-described findings in Alport syndrome—an inherited condition also caused by mutations in type IV collagen. The literature on bilateral posterior lenticonus is scarce, however, and the specificity of the radiographically defined posterior lenticonus to type IV collagen disorders is unknown.

As mentioned, it has been reported that 22% of *COL4A1* patients have congenital cataracts. However, the types of cataracts were not reported. These 2 *COL4A1* patients presented with subtle posterior cataracts that are likely posterior lenticonus-related opacities. We suggest that bilateral posterior opacities and posterior lenticonus in the context of porencephaly should raise clinical suspicion for *COL4A1* mutations. Importantly, although our cases manifested porencephaly, previous *COL4A1* case reports have described broader neurovascular pathology.[2,4,5]

These 2 cases highlight the importance of a comprehensive systemic evaluation in the context of bilateral congenital cataracts. They also emphasize the role of pediatric ophthalmologists in the diagnosis of *COL4A1* mutations. Appropriate recognition is not only important for recurrence risk counseling but also for identifying paucisymptomatic carrier family members at risk for intracranial bleeding. Further studies are needed to determine whether these phenotypic characteristics are consistent findings in *COL4A1* mutations.

Literature Search

PubMed and MEDLINE were searched without date restriction in May 2018 using the terms: *COL4A1 mutation* OR *porencephaly* OR *posterior lenticonus* AND *type IV collagen mutations*.

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