Nonleaking cystoid macular edema in Cohen syndrome

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An 11-year-old girl with a history of neutropenia, developmental delay, hypotonia, and intellectual disability was diagnosed with Cohen syndrome after genetic testing discovered homozygous mutation in the *VPS13B* gene. She was referred to a retinal specialist with a chief complaint of decreased peripheral vision. On examination, decreased visual acuity, pigmentary changes, and nonleaking cystoid macular edema were present in both eyes.

Cohen syndrome is a rare autosomal recessive disorder that is commonly underdiagnosed in patients with unexplained development delay. It is characterized by failure to thrive in infancy, truncal obesity in the teen years, early-onset hypotonia, developmental delays, microcephaly, moderate to profound psychomotor retardation, progressive retinochoroidal dystrophy and high myopia, hypermobility, neutropenia with recurrent infections and aphthous ulcers, cheerful disposition, and characteristic facial features.[1] The diagnosis is made based on clinical features and can be confirmed with genetic testing identifying pathogenic variants in *VPS13B*.[1]

Chandler and colleagues[2] assessed 33 patients from 1999 to 2001. All had visual abnormalities, with progressive myopia and progressive pigmentary retinopathy being the most common; 35% of patients were registered as partially sighted or blind. Astigmatism, strabismus, microcornea, microphthalmia, sluggish pupillary reaction, iris atrophy, lens opacities, lens subluxation, optic atrophy, bull's eye maculopathy, coloboma of the retina or eyelids, ptosis, exophthalmos, poor visual acuity, nyctalopia, and constricted visual fields have also reported. Retinal dystrophic changes are slow, unfolding over the course of decades. Useful vision is usually preserved until the fourth decade.[3-5]

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Case Report

A 3-year-old girl diagnosed with benign neutropenia of childhood in 2009 later developed a papular rash with occasional pustules along with swollen gingiva with ulcerative lesions in her buccal mucosa, prompting a bone marrow aspiration with biopsy in 2012. The biopsy revealed adequate neutrophil precursors with complete maturation, without evidence of myelodysplasia or leukemia. She was started on filgrastim, which has controlled her neutrophil count. In 2014 a metabolic genetics specialist ordered whole-genome sequencing, which revealed the presence of a homozygous c.6732+1G>A mutation in the *VPS13B* gene leading to the clinical diagnosis of Cohen syndrome.

On September 28, 2017, the patient presented at Austin Retina Associates for retinal consultation. The patient's mother reported that the child had decreased peripheral vision and photophobia. On examination, visual acuity was 20/200 in the right eye and 20/80 in the left eye. Bilateral exotropia was present. Intraocular pressure, pupils, ocular motility, and anterior segment examination were within normal limits. Posterior examination was notable for pigmentary changes in the macula and periphery in both eyes. Optical coherence tomography (OCT) revealed cystoid macular edema (CME; eFigure 1). A topical carbonic anhydrase inhibitor—dorzolamide 2%—was initiated. Examination under anesthesia with fluorescein angiography (FA) showed nonleaking CME (Figure 1; see also eFigure 2). On follow-up examination on December 7, 2017, the patient's vision, macular appearance, and OCT were stable. Continuation of dorzolamide for 3-6 months was recommended.

Discussion

Genetic testing is valuable in diagnosing or confirming the diagnosis of Cohen syndrome by identifying pathogenic variants in *VPS13B*, which encodes a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport.[6] *VPS13B* is necessary for structural maintenance and function of the Golgi apparatus, including glycosylation of proteins. This interference with normal Golgi function[7] may explain our patient's symptomatic neutropenia along with her development delay, intellectual disability, and hypotonia.

Pigmentary dystrophies have been associated with Cohen syndrome.[8] Cystic changes without leakage on FA are seen in a number of retinal dystrophies, including retinitis pigmentosa, enhanced S cone syndrome, and X-linked retinoschisis.[8] In retinal dystrophies, it has been proposed that macular cysts develop because of tissue loss secondary to disruption of retinal architecture in the macular region; vasculature leakage is thought to play a minor role, if any, given the normal appearance of the macular on angiography.[9,10] In retinitis pigmentosa, the macular edema is thought to be secondary to failure of the retinal pigment epithelium (RPE) pump or toxic products liberated from degenerating retina. In juvenile X-linked retinoschisis there is mutation of the *RS1* gene, which encodes the

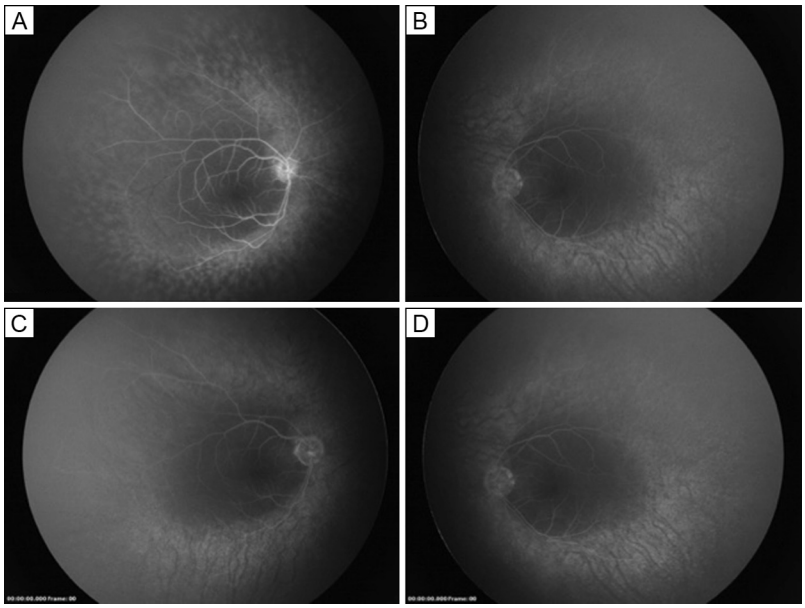

FIG 1. Early-phase fluorescein angiography of right eye (A) and left eye (B). Late-phase fluorescein angiography of the right eye (C) and left eye (D). Leakage in the macula in both eyes was absent.

protein retinoschisin. This results in impaired adhesion and splitting of the retinal layers. In enhanced S cone syndrome, there is mutation of the *NR2E3* gene, which results in abnormal rods that have features of cones[9]; this is thought to result in the inability to form tight junctions. In immunohistochemical studies, carbonic anhydrase is present in the wall of the RPE. It is therefore thought to be important in the regulation of fluid movement across the RPE. Inhibition of carbonic anhydrase activity has been shown to increase fluid movement from the retina across the RPE to the choroid and to strengthen retinal adhesiveness. Carbonic anhydrase inhibitors and intravitreal corticosteroids have been shown to be effective in reducing macular edema and subsequently are mainstay treatments for cystic changes in the setting of retinal dystrophies.[8-10]

No specific cause of vision loss has been noted in patients with Cohen syndrome. The finding of nonleaking CME provides a possible explanation. In addition, it may provide a platform for future gene therapy trials. To our knowledge, this is the first report of a case of nonleaking CME in a patient with Cohen syndrome.

Literature Search

PubMed was searched in December 2017 for English-language results using the following terms: *Cohen syndrome*, *Cohen syndrome CME*, and *pigmentary retinopathy CME*.

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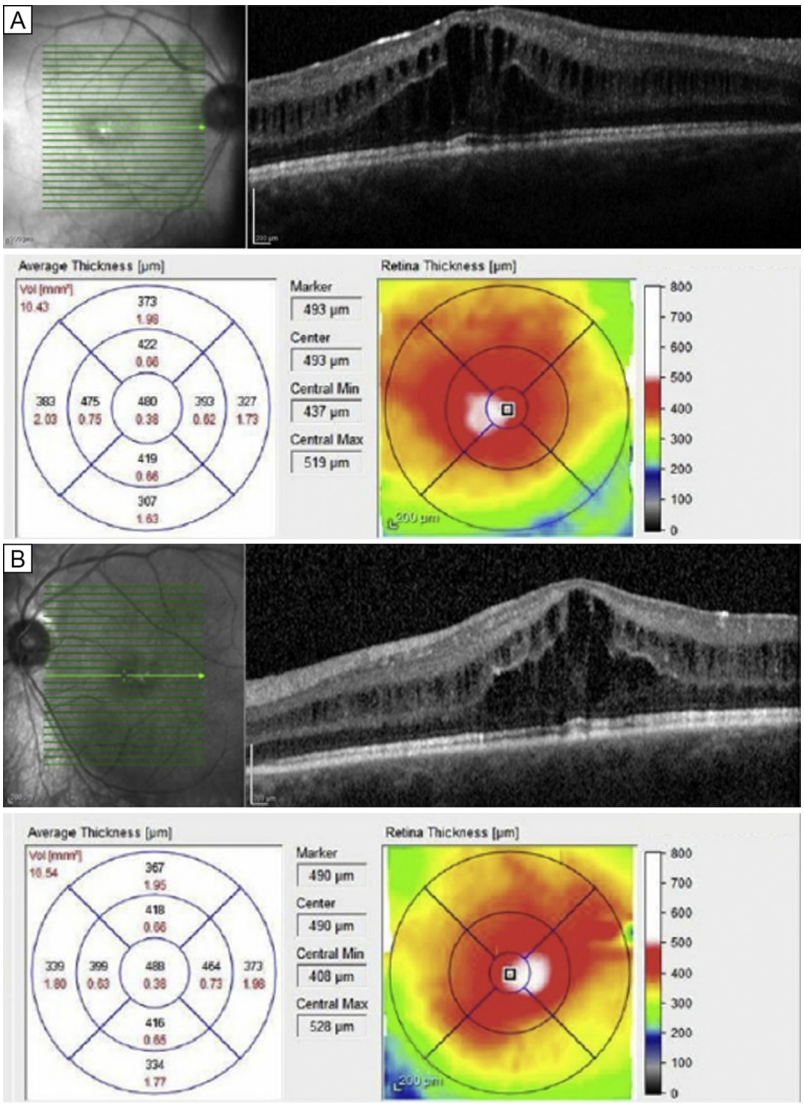
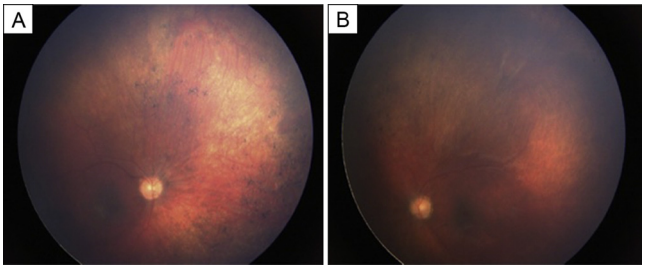


eFIG 1. Optical coherence tomography showing macular cysts in the right eye (A) and left eye (B) on September 28, 2017.



eFIG 2. Fundus photography of the right eye and left eye with pigment changes of the macula and in the periphery.