JAMA Ophthalmology Clinical Challenge

Bilateral Retinal Nerve Fiber Layer Thickening in a Middle-Aged Woman

Ivy Zhu, MD; Amani A. Fawzi, MD

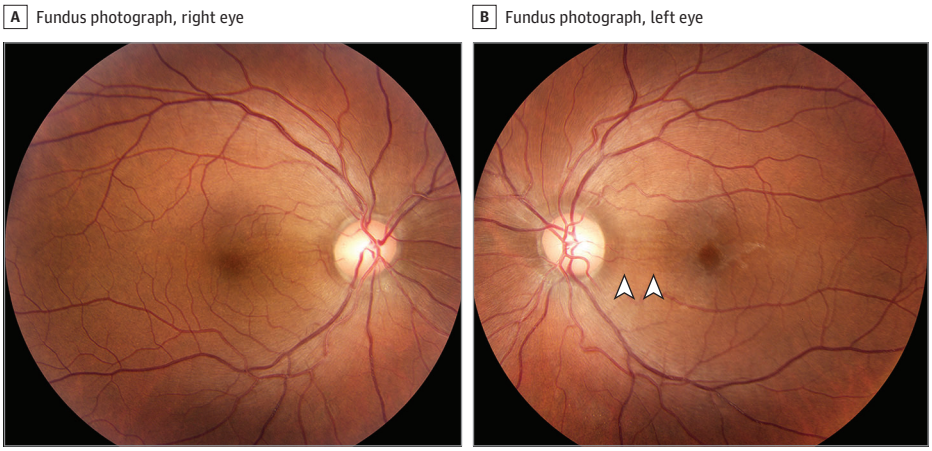

Figure 1. Fundus photograph of the right and left eye. Note the prominent retinal nerve fiber layer radiating from the optic nerve in a sunburst appearance. There are also fine striae in the papillomacular bundle of both eyes, most pronounced in the left eye (arrowheads).

A Hispanic woman in her 40s was referred for an asymptomatic epiretinal membrane in the left eye. Ocular history included amblyopia of the left eye. Medical history included chronic neuropathy, ataxia, and myelopathy of unknown etiology for which she was followed up by a neurologist. Family history was positive for consanguinity, but there were no known inherited conditions. Genetic testing showed a homozygous variant of undetermined significance in the *SACS* gene and a variant of undetermined significance in the *SLC5A7* gene, but it was inconclusive whether these variants were related to her systemic conditions. Review of systems was otherwise negative.

On initial examination, best-corrected visual acuity was 20/30 OD and 20/100 OS. Intraocular pressure, pupils, anterior segment, and visual fields were normal bilaterally. Extraocular movements were saccadic with gaze-evoked horizontal nystagmus. Fundus examination revealed prominent peripapillary retinal nerve fibers with papillomacular bundle fine striae and slightly blunted foveal light reflex. There was also an irregular sheen of the nasal macula in both eyes, greater in the left eye (**Figure 1**). Axial length was 22.93 mm in the right eye and 22.10 mm in the left eye, with anterior chamber depth of 3.44 mm and 3.37 mm in the right and left eye, respectively.

WHAT WOULD YOU DO NEXT?

A. Obtain an electroretinogram

B. Obtain optical coherence tomography of the macula and retinal nerve fiber layer

C. Schedule pars plana vitrectomy with membrane peeling

D. Obtain visual field testing

CME Quiz at jamacmelookup.com

Diagnosis

Autosomal recessive spastic ataxia of Charlevoix-Saguenay

What to Do Next

B. Obtain optical coherence tomography (OCT) of the macula and retinal nerve fiber layer (RNFL)

Discussion

The patient's medical and family history and abnormal genetic testing suggest a hereditary spastic ataxia, most likely related to the *SACS* gene variant, which causes autosomal recessive spastic ataxia of Charlevoix-Saguenay (AR-SACS). Obtaining an OCT of the macula and RNFL (option B) is the next best step to confirm AR-SACS, which presents with specific retinal findings of fovea plana and thickened peripapillary RNFs associated with papillomacular folds.[1] Electroretinogram and visual field abnormalities (options A and D, respectively) are not specific to AR-SACS and can be found in other ataxias. Pars plana vitrectomy with membrane peeling (option C) is not indicated given the patient's lack of symptoms.

AR-SACS is the second most common hereditary ataxia after Friedrich ataxia and often presents in childhood at 12 to 18 months with the initiation of walking.[2] Patients may develop a classic triad of progressive cerebellar ataxia, spasticity, and sensorimotor peripheral neuropathy. Magnetic resonance imaging may show supe-

rior vermis and cerebellar hemisphere atrophy, linear hypointensities in the paramedian pons, hyperintense lateral pons, and thickened middle cerebellar peduncles.

The condition is due to a *SACS* gene variant on chromosome 13q12, which produces the sacsin protein that helps regulate microtubule function in brain, skin, and muscle cells.[3,4] The incidence is approximately 1 in 2000 in the Charlevoix-Saguenay region of northeastern Québec, where the disease was initially described, but the prevalence of AR-SACS outside this area is unknown. Reported cases of AR-SACS outside the original Québecois cohort have increased with advances in genetic sequencing. Notably, these patients often present with greater clinical variability and variants of unknown significance in the *SACS* gene, as in this patient.[5]

In suspected cases of AR-SACS, the ophthalmologist can play an important role in confirming or making the diagnosis. Nonprogressive signs include saccadic eye movements, horizontal gaze-evoked nystagmus, fovea plana, and RNFL thickening.[1] RNFL thickening classically appears as a sunburst radiating from the optic nerve. OCT macula and RNFL show a thickened peripapillary RNFL that is virtually pathognomonic for AR-SACS. This is in contrast to other ataxias that universally demonstrate RNFL thinning.[6,7] In a cross-sectional study involving 191 patients with ataxias of various etiologies and 101 controls, a cutoff value of bilateral mean peripapillary RNFL thickening greater than 119 µm was 100% sensitive and 99.4% specific for AR-SACS.[8] Some authors suggest the RNFL thickening may be due to hyperplasia or hypertrophy rather than myelination, with associated mild to severe nonspecific visual field deficits.[9]

Additional OCT findings include foveal hypoplasia (100%), sawtooth appearance of the outer plexiform layer (89%), papillomacular fold (86%), and macula microcysts (18%).[1] Papillomacular folds and fovea plana are commonly reported features of posterior microphthalmos, where the axial length is shorter than 23.5 mm but the anterior chamber depth is normal (approximately 3.5 mm).[10] This patient's macular findings are consistent with posterior microphthalmos, which may unify the retinal findings in patients with AR-SACS. However, this finding has not previously been reported, and more research is needed to confirm this relationship.

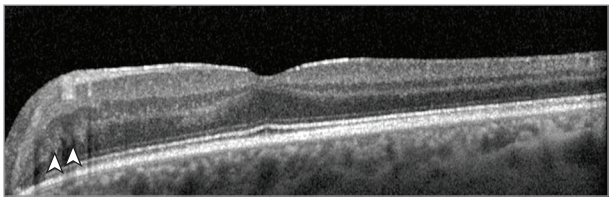

Figure 2. Optical coherence tomography (OCT) of the macula demonstrating thickness in the nasal peripapillary region and sawtoothed appearance to the papillomacular bundle (arrowheads) and fovea plana.

Recognition of these specific retinal findings in a patient with symptoms of ataxia and neuropathy can provide a diagnostic clue to AR-SACS and help narrow the genetic workup of these patients.

Patient Outcome

OCT of the macula and RNFL were obtained, showing foveal hypoplasia, sawtooth appearance of the outer plexiform layers, and thickening of the peripapillary RNFL (**Figure 2**), with a mean thickness of 187 µm and 178 µm in the right and left eye, respectively. The confirmatory ocular findings were communicated with the referring neurologist, along with continued observation.

ARTICLE INFORMATION

Author Affiliations: Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Corresponding Author: Amani A. Fawzi, MD, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, 645 N Michigan Ave, Chicago, IL 60611 (afawzimd@gmail.com).

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