JAMA Ophthalmology Clinical Challenge

A Young Boy With Changes in the Retinal Pigment Epithelium

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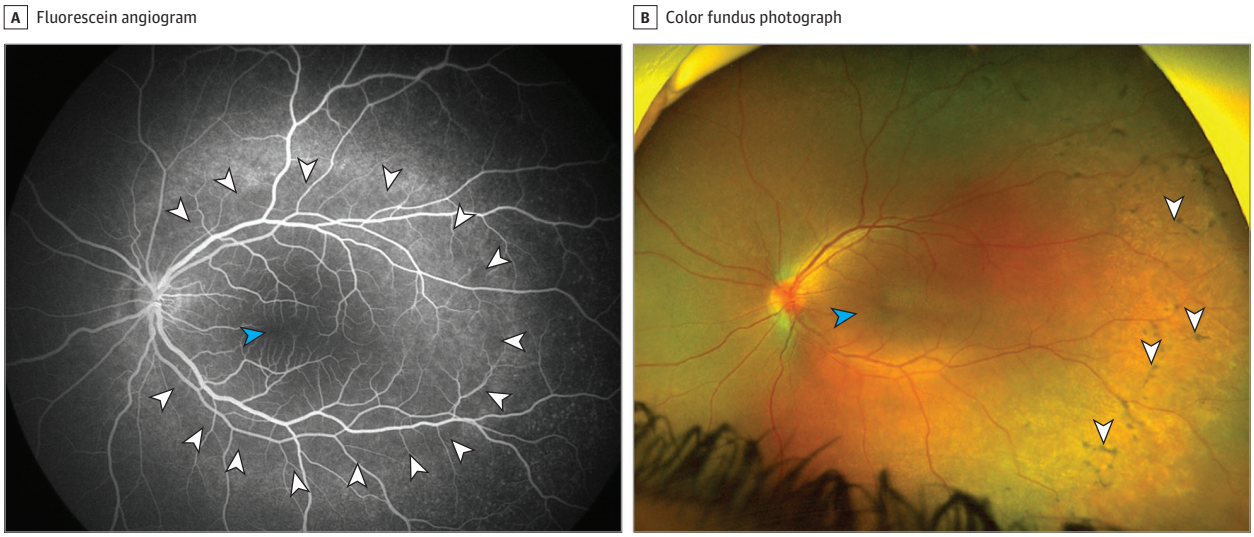

Figure 1. Fluorescein angiogram and color fundus photograph. A, Fluorescein angiography of the left eye revealed a circular area of hypofluorescence encompassing the macula (white arrowheads) and an irregular fovea (blue arrowhead), likely representing a thickened choroid secondary to a horizontal papillomacular fold. B, Color fundus photograph disclosed peripheral retinal pigment epithelium mottling (white arrowheads) and a densely pigmented small macula (blue arrowhead).

A 9-year-old boy was referred to a pediatric retina specialist for evaluation of changes in the peripheral retinal pigment epithelium. Ocular history included high hyperopia and amblyopia, and abnormal foveal contour was discovered when he was aged 3 years. Family history was noncontributory. Best-corrected visual acuity was 20/50 in the right eye and 20/30 in the left. Pupils were round and reactive to light, and intraocular pressure and anterior segment examination were within normal limits. Dilated fundus examination revealed blunted foveal reflexes and abnormal vasculature in the inferonasal quadrant of the right eye. Fluorescein angiography displayed symmetric bilateral circular areas of hypofluorescence around the macula and irregular fovea with no leakage (**Figure 1**A). Color fundus photography showed symmetric bilateral mottling of the retinal pigment epithelium in the periphery (Figure 1B). Spectral-domain optical coherence tomography on initial examination showed an abnormal foveal contour with loss of the foveal pit and intraretinal cystoid cavities within the inner nuclear layer.

WHAT WOULD YOU DO NEXT?

- **A.** Perform B-scan ultrasonography
- **B.** Genetic testing to assess for ocular diseases
- **C.** Observation
- **D.** Obtain fundus autofluorescence

Quiz at jamacmelookup.com

Diagnosis

Congenital nanophthalmos

What to Do Next

B. Genetic testing to assess for ocular diseases

Discussion

Nanophthalmos, which affects ocular development, is the most prevalent genetic congenital ocular disorder.[1,2] It is characterized phenotypically by small eyes and normally presents without associated structural defects[1] and with high hyperopia secondary to severely decreased axial length.[3] Mean best-corrected visual acuity ranges from 20/25 to 20/50.[4] Posterior involvement can lead to an irregular fovea (Figure 1), papillomacular folds, abnormal foveal contour, and uveal effusions. Patients with nanophthalmos have an increased risk of developing acute angle-closure glaucoma, retinal detachment, and intraretinal cysts (**Figure 2**).[2] The schisislike cystoid thickening of the retina has been proposed to arise from crowding of the retina and uveal tissues and poor outflow through the characteristically thickened sclera. Although literature on the angiographic characterization of this phenomenon is limited, fundus autofluorescence is not expected to show leakage surrounding these spaces.[5,6]

Nanophthalmos can be inherited in an autosomal dominant or recessive fashion or from sporadic genetic derangements that interfere with the normal formation of the optic cup.[1,2] Depending on the presence of ocular and systemic manifestations, nanophthalmos can be isolated, complex, or syndromic.[2,7] The gene most implicated with nanophthalmos is the membrane-type frizzled-related protein gene (*MFRP*), also associated with retinal dystrophy.[2,3] *MFRP* encodes for a transmembrane protein highly expressed in the retinal pigment epithelium and ciliary body and plays an important role in eye development prenatally and postnatally, with the only progressive change mentioned in the literature being amblyopia when axial hyperopia is left untreated in nanophthalmos.[1]

The genetic etiology of the severe hyperopia in this patient remained unrecognized until he was referred to a pediatric retina specialist to rule out retinitis pigmentosa. At that point, the patient had considerable posterior segment involvement causing abnormal foveal and papillomacular folds, retinal pigment epithelium mottling (Figure 1), and intraretinal cysts (Figure 2). This constellation of findings along with axial lengths of 17.8 mm in the right eye and 17.7 mm in the left eye triggered genetic testing.

Genetics for ocular diseases (B) is the correct answer because other conditions have similar presentation to nanophthalmos, making genetic testing the more certain way to diagnose it. If no mutation is found, this can also help rule out similar-appearing ocular genetic diseases.

Although B-scan ultrasonography (A) would be helpful to confirm decreased axial length, suggestive of nanophthalmos,[8] it does not provide enough information to rule out other diseases or confirm the diagnosis. Observation (C) alone is not appropriate. Although the findings suggest nanophthalmos, further investigation is needed to diagnose the condition, provide treatment as necessary, and be aware of potential complications. Finally, fundus autofluorescence (D) would likely show macular changes associated with the cystoid retinal thickening; however, it would not be enough to make a definitive diagnosis, and genetic testing would still be necessary.[2]

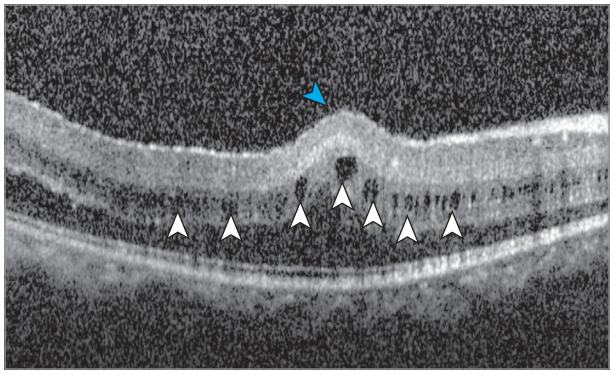

Figure 2. Optical coherence tomography of the macula. Spectral-domain optical coherence tomography showed an abnormal foveal contour with loss of the foveal pit (blue arrowhead) and intraretinal cystoid cavities within the inner nuclear layer (white arrowheads).

Patient Outcome

This patient underwent genetic testing revealing 2 pathogenic variants in the *MFRP* gene, confirming the diagnosis of autosomal recessive nanophthalmos and retinal dystrophy. The mother was informed about the condition and its prognosis. The patient underwent amblyopic management, is being monitored biannually, and has remained visually stable.

ARTICLE INFORMATION

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