What to Look for With MODY

Maturity-onset diabetes of the young–a rare monogenic variant–can present with a severe form of diabetic retinopathy.

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Extensive literature exists detailing the effect of both type 1 diabetes mellitus (DM; mediated by insulin deficiency due to autoimmune destruction of pancreatic beta cells) and type 2 DM (mediated by insulin resistance) on the retina.[1] However, there is a paucity of data on the pathologic retinal changes due to maturity-onset diabetes of the young (MODY).

MODY is a rare cause of DM contributing to approximately 1% of all cases.[2] It can manifest in childhood, adolescence, or early adulthood.[2] Unlike type 1 or 2 DM, MODY is monogenic, with at least 14 known gene mutations. The four most common are in *hepatic nuclear factor 1 alpha* (*HNF1A*), *HNF4A*, *HNF1 beta*, and *glucokinase* (*GCK*). Each mutation affects insulin production differently, which determines the systemic manifestations and treatment approach. For example, *GCK*-MODY has minimal insulin-level perturbations and systemic microvascular sequelae, while *HNF1A*-MODY causes worse pancreatic beta cell dysfunction, decreased insulin production, and more severe systemic sequelae.[3]

Herein, we present a rare case of a young "healthy" patient with a family history of MODY and rapid onset of proliferative diabetic retinopathy (PDR).

THE CASE

A 32-year-old White man was referred for progressive decrease in vision in his right eye. He denied any previous medical history except for a diagnosis of diabetes 6 months prior. His brother and several family members over two generations were diagnosed with diabetes in their 20s and 30s. His brother had been diagnosed with MODY (genetically confirmed, unknown mutation) 5 years prior. Initially, the patient had a reported hemoglobin A1c of > 10% that had an excellent response to metformin and glipizide.

On examination, BCVA was 20/800 OD and 20/25 OS, with no relative afferent pupillary defect, normal IOPs, and no neovascularization of the iris. Dilated fundus examination revealed cotton-wool spots, dot-blot hemorrhages, microaneurysms, and neovascularization elsewhere in the right eye and early neovascularization elsewhere, cotton-wool spots, and dot-blot hemorrhages in the left eye (Figure 1). OCT imaging showed significant macular edema and disruption of the subfoveal ellipsoid zone (EZ) in the right eye and minimal cystoid macular edema in the left eye.

Fluorescein angiography (FA) was notable for large swaths of hypofluorescence suggestive of peripheral capillary nonperfusion, leakage from neovascularization, and blockages from the dot-blot hemorrhages in the right eye (Figure 2). Critically, there was also an enlarged foveal avascular zone (FAZ). In the left eye, there was a lesser but still significant amount of peripheral capillary nonperfusion, areas of leakage from neovascularization, and a normal FAZ.

Given the PDR and macular edema, the patient underwent anti-VEGF injections in each eye at presentation, followed by panretinal photocoagulation in each eye.

At the 1-year follow-up, VA had improved to 20/100 OD and 20/20 OS. The macular edema and peripheral neovascularization had resolved. OCT imaging showed significant

AT A GLANCE

- Maturity-onset diabetes of the young (MODY) contributes to roughly 1% of all diabetes cases.
- The underlying genetic mutations play an important role in the phenotypic manifestations of MODY-associated retinopathy, which underscores the importance of genetic testing.
- Chronic hyperglycemia in MODY can lead to microvascular damage with subsequent decreased perfusion and increased risk of neovascularization.

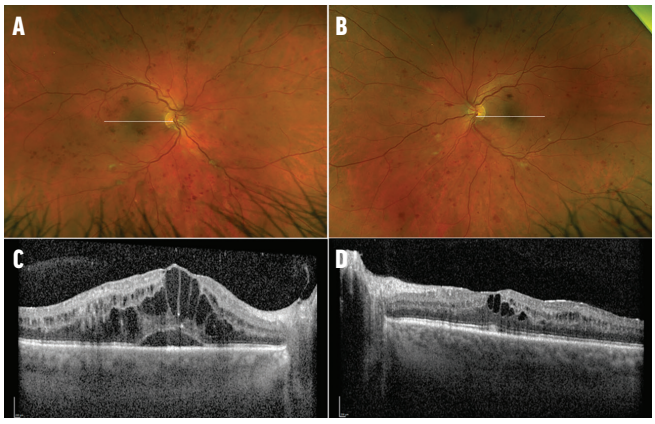

Figure 1. Widefield imaging reveals dot-blot hemorrhages in all quadrants, hard exudates, cotton-wool spots, and neovascularization elsewhere in the right eye (A). The left eye has less severe proliferative retinopathy with dot-blot hemorrhages, cotton-wool spots, and early neovascularization elsewhere (B). The white lines correspond to the OCT segmentation at the fovea. OCT of the right eye shows significant macular edema and disruption of the fovea (C). The left eye has minimal cystoid macular edema (D).

diffuse perifoveal attenuation of the EZ in the right eye and scattered macular exudates with subtle subfoveal attenuation of the EZ in the left eye (Figure 3).

DISCUSSION

MODY is a rare form of diabetes caused by a single genetic mutation.[4] Unlike type 1 or 2 DM, there is no autoimmune pancreatic beta cell death nor insulin resistance. MODY should be suspected in patients younger than age 30 with persistent hyperglycemia, clinical features not usual for type 1 or 2 DM, and a family history of diabetes. After obtaining various serologies to rule out ancillary disorders, genetic testing is ultimately necessary to confirm the diagnosis.[5,6]

There are currently 14 known gene mutations that cause MODY,[7] but *HNF1A* and *GCK* account for roughly 80% of cases.[8] *HNF1A* is a transcription factor prominent in hepatic and pancreatic tissues that helps regulate beta cell function.[9] Mutations in *HNF1A* cause progressive beta cell dysfunction, reduced glucose-stimulated insulin secretion, and low renal threshold for glucosuria.[9] *GCK* catalyzes adenosine triphosphate-dependent phosphorylation of glucose to produce glucose-6-phosphate, which is the rate-limiting reaction of glucose metabolism.[2] Mutations in *GCK* have minimal clinical effects and rarely require treatment, except in pregnancy.[2,10] In contrast to *HNF1A*-MODY, microvascular complications are much less prevalent in *GCK*-MODY.[9]

Like both type 1 and 2 DM, chronic hyperglycemia in MODY can lead to microvascular damage with subsequent decreased perfusion and increased risk of neovascularization. In one study, investigators developed an *HNF1A*-MODY porcine model and monitored the development of DR using fundus photography and fluorescein angiography. They found that *HNF1A*-MODY eyes developed greater vascular tortuosity, decreased blood vessel density, and thickening

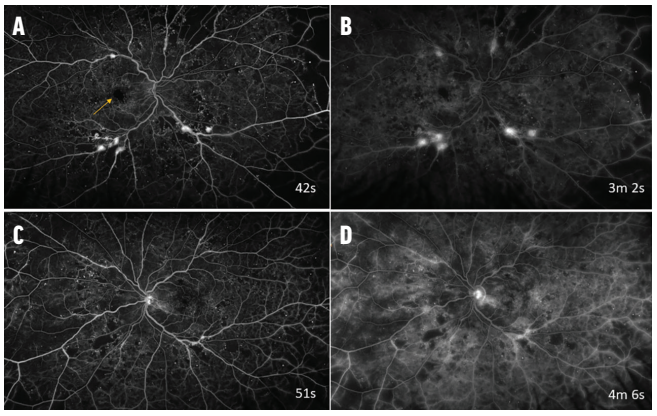

Figure 2. The early frame widefield FA of the right eye shows an enlargement of the FAZ (A, yellow arrow), significant peripheral nonperfusion and vessel attenuation, and early leakage corresponding to areas of neovascularization elsewhere. The later frame delineates the neovascularization elsewhere and demonstrates a persistent FAZ enlargement (B). The left eye shows microaneurysms and peripheral nonperfusion but no evidence of FAZ enlargement (C). The late frame demonstrates the overall capillary attenuation, given the patchy staining throughout the retina (D).

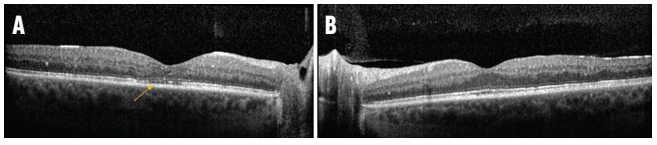

Figure 3. OCT of each eye at 1 year. The right eye shows persistent subfoveal EZ attenuation (yellow arrow) and foveal thinning (A). The left eye shows resolution of the macular edema (B).

of capillary basement membranes compared with wild-type pig eyes.[11] The data overall suggest a similar mechanism as vascular complications due to type 1 or type 2 DM.

The underlying genetics of MODY contribute to their differences in retinal manifestations. There is a paucity of data on MODY-induced DR. In a case series from 2015, only one of 51 patients with *GCK*-MODY had findings of mild NPDR. In contrast, 15 of 63 patients with *HNF1A*-MODY had findings of DR, including nine patients with PDR with high-risk characteristics.[12] A case report of a 32-year-old man with presumed MODY developed PDR early, but after treatment and glucose control, his retinopathy was stable for approximately 30 years without progression.[13] The underlying mutations play an important role in the phenotypic manifestations of DR, underscoring the importance of genetic testing.

Our patient's clinical course provides further insight into this rare form of diabetes. First, he exhibited findings of advanced disease at presentation. Despite annual follow-ups, he developed PDR in a relatively short amount of time. However, he had a robust systemic response to metformin and sulfonylureas with improvement in hemoglobin A1c from > 10% to 7% within several months.

At 1 year, VA had improved to 20/100 OD, which, although better than presentation, represents the significant changes of hyperglycemic microvascular complications and resultant macular ischemia. At the most recent visit, OCT

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imaging demonstrated stable perifoveal attenuation of the outer retinal layers in the right eye. The patient underwent genetic testing, which revealed a single exon deletion in *HNF4A*, a known autosomal dominant pathogenic variant.

IMPORTANT CLINICAL PEARLS

Although type 1 and 2 DM are the main drivers of DR, less common types such as monogenic forms of MODY can also present to our clinics. Obtaining a thorough history can be difficult, but it is invaluable. MODY-associated DR is rare, and the phenotypic changes depend on the specific mutation. Early genetic screening of these patients and their family can help with understanding the prognosis, direct treatment, and guide the timing for follow-up visits to mitigate the development of severe microvascular complications. ■

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