Case Report

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Retinal Pigment Epithelial Defects and Vascular Anomalies in a Patient with Gilbert Syndrome

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ABSTRACT

Purpose: To report a unique case of retinal pigment epithelium (RPE) defects and venous abnormalities in an adolescent patient with Gilbert syndrome.

Methods: The patient underwent comprehensive ophthalmic evaluation including optical coherence tomography (OCT), fundus photographs, intravenous fluorescein angiography (IVFA).

Results: A 16-year-old male with Gilbert syndrome was referred for evaluation of unilateral retinal pigmentary changes discovered in the right eye during routine optometric eye examination. Bilateral IVFA demonstrated areas of temporal capillary non-perfusion in the far periphery slightly anterior to areas of RPE hypopigmentation in a curvilinear pattern. Atypical anastomosis of peripheral vasculature was noted in the left eye with venous remodeling. No new changes in visual acuity or retinal appearance were noted at three-month follow-up.

Conclusion: This constellation of retinal anomalies including venous abnormalities and areas of RPE hypopigmentation may be attributed to the transient indirect hyperbilirubinemia of Gilbert syndrome. Bilirubin is known to play a role in angiogenesis as well as having both anti- and pro- oxidant effects in neural tissue.

Introduction

Gilbert syndrome is a common hereditary condition characterized by dysfunctional metabolism of bilirubin in the liver. Bilirubin is a breakdown product of heme, and the most notable complication of hyperbilirubinemia is neonatal neurotoxicity in the form of kernicterus. It is most often inherited in an autosomal recessive pattern but may be autosomal dominant depending on the genetic variant, with prevalence ranging from 2% to 20% among different ethnicities.1 In the Caucasian population, Gilbert syndrome is most often associated with the homozygous polymorphism A(TA)7TAA mutation in the promoter region of UGT1A1, though over 100 mutations have been associated with this syndrome, including polymorphisms of the UGT1A1 TATA box and UGT1A1 coding exon 1 in African and Asian populations, respectively.1 In this disorder, impaired bilirubin glucuronidation leads to unconjugated hyperbilirubinemia with recurrent episodes of jaundice in otherwise asymptomatic patients.1 These episodes are commonly precipitated by stressors such as fasting, fever, hemolytic disease, physical exertion, and menstruation.2 While the typical presentation of Gilbert syndrome is well-characterized, no studies have demonstrated potential manifestations of this syndrome in the retina.

Case Presentation

A 16-year-old Caucasian male with a history of Gilbert syndrome was referred for evaluation of unilateral retinal pigmentary changes discovered in the right eye during routine optometric eye examination. Other than known Gilbert syndrome and moderate bilateral myopia, his past ocular history, past medical history, and family history were unremarkable. His medications included Adderall 5 mg, Citalopram 10 mg, Mirtazapine 30 mg, and a multivitamin with minerals 9 mg iron / 15 mL oral liquid. He denied any changes to vision or other symptoms.

At time of examination, best corrected visual acuity was 20/15 in both eyes at distance and near. Manifest refraction was -6.00 -0.25 x 009 and -5.75 -1.00 x 162 for the right and left eyes, respectively. Extraocular muscles were intact. Pupils were round,

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reactive to light and accommodation, with no afferent pupillary defect. External examination and slit lamp evaluation of the anterior segment were within normal limits. Intraocular pressures were 19 mmHg and 18 mmHg by tonometry in the right and left eyes. Dilated fundus examination of the right eye revealed a tilted optic disc, inferior lattice degeneration, congenital hypertrophy of the retinal pigment epithelium (CHRPE) superotemporally and, most notably, a clearly defined area of retinal pigment epithelium (RPE) hypopigmentation in the far temporal periphery with an area of avascular retina peripherally (Figure 1). Evaluation of the left eye demonstrated similar findings of a tilted optic disc and two temporal areas of venous anastomoses posterior to large areas of avascular retina (Figure 2).

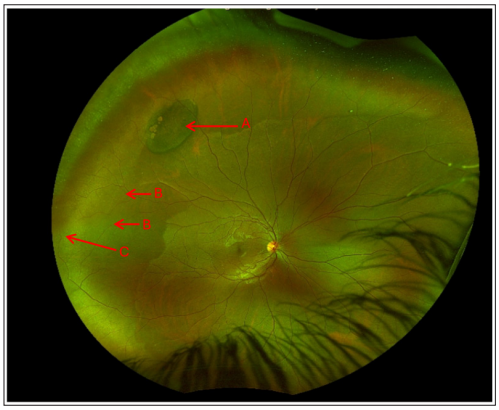

Figure l: Color fundus photo of right eye with area of CHRPE superotemporally (A), and RPE curvilinear hypopigmentation (B). Anterior retina temporally is somewhat avascular (C).

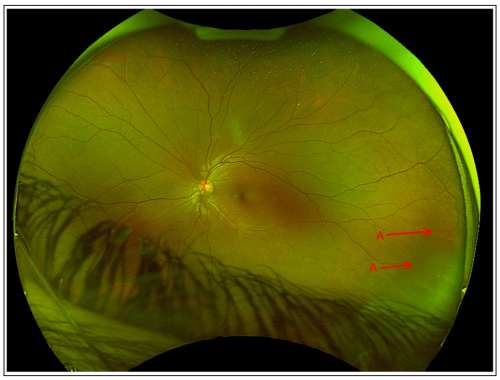

Figure 2: Color fundus photo of left eye with subtle venous anastomoses (A).

Ishihara color plates and stereopsis testing revealed no abnormalities. Humphrey visual field (HVF) testing was normal and optical coherence tomography (OCT) was unremarkable. Intravenous fluorescein angiography (IVFA) bilaterally showed areas of temporal capillary non-perfusion in the far periphery next to the noted areas of RPE hypopigmentation in a curvilinear pattern in the right eye (Figure 3). Atypical anastomosis of peripheral venous vasculature was noted in the left eye with venous remodeling (Figure 4). No evidence of vascular leakage or inflammation was noted.

At three-month follow-up, best corrected visual acuity (BCVA) was stable, and exam was unchanged. The patient underwent prophylactic laser photocoagulation to areas of lattice degeneration in the right eye without incident.

Figure 3: IVFA of the right eye with a superior area of CHRPE (A) with typical RPE alterations. There is a curvilinear area of retinal pigment epithelial loss (B) and large area of avascular retina anterior to the pigment loss (C).

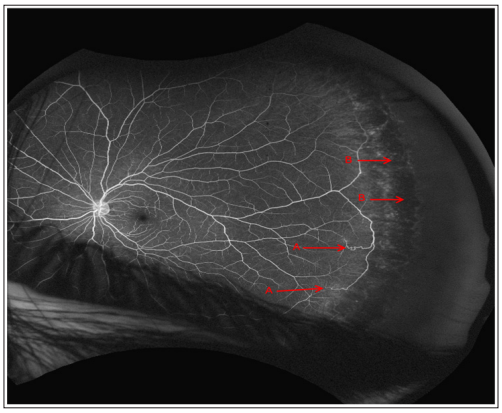

Figure 4: IVFA of left eye demonstrating two venous anastomoses (A) and a large area of avascular anterior retina (B).

Discussion

Gilbert syndrome is a systemic disorder of unconjugated hyperbilirubinemia without reported retinal manifestations. Bilirubin, traditionally thought to be a hemoglobin waste product, has several important physiological properties beyond its catabolic origin. Over the past 30 years, multiple studies have demonstrated that bilirubin serves as a potent antioxidant pathways, and angiogenesis [3–6].

Previous studies analyzing the effects of bilirubin on the retina have largely focused on its protective antioxidant role in retinopathy of prematurity (ROP), a vasoproliferative retinal disease driven by oxidative stress which affects preterm infants.7 Furthermore, fluctuations in systemic bilirubin levels are known to be reflected in the retina and animal models have been used to demonstrate a potential protective effect of bilirubin against photoreceptor cell death.8 Other studies have demonstrated a dose-dependent effect, with higher concentrations of bilirubin having toxic pro-oxidant effects on neurons and glial cells.6 Therefore, patients with Gilbert syndrome who experience fluctuations in systemic unconjugated bilirubin levels may be susceptible to both the toxic and protective effects of bilirubin in the retina. Due to the immaturity of the blood–brain barrier in children, the effect of episodic indirect hyperbilirubinemia on neurodevelopment is significantly greater in early life than in adulthood.6 Furthermore, bilirubin has been demonstrated to

inhibit the function of various enzymes including hydrolases, which are an essential component of the lysosome-mediated autophagy of various photoreceptor waste products.9,10 The authors propose this as a potential mechanism underlying the RPE defects and vascular remodeling demonstrated in the eyes of the patient.

In addition to the dose-dependent anti- or pro-oxidant effects, bilirubin is a known driver of angiogenesis. One proposed mechanism for the role of bilirubin in angiogenesis is modulation of the PI3K/AKT pathway which activates endothelial nitric oxide synthase.4 Furthermore, heme oxygenase (HMOX-1), an enzyme that converts hemoglobin to biliverdin upstream of bilirubin production, is known to upregulate VEGF and IL-8.3,5 This may explain the anomalous venous anastomoses observed in the temporal retina of the left eye in this patient. However, to our knowledge, no previous cases of similar retinal venous anastomoses have been reported in other conditions involving hyperbilirubinemia such as neonatal cholestasis or biliary atresia.

Conclusion

Bilirubin is known to have pro- and anti-oxidant effects as well as a role in angiogenesis. These effects have been demonstrated to impact neuronal and glial tissues, which would include the retina. Thus, patients with Gilbert syndrome who experience transient episodes of hyperbilirubinemia may have evidence of RPE defects and retinal vascular anomalies on fundus examination. While further studies are necessary to elucidate the exact mechanism underlying these retinal findings in Gilbert syndrome, this case presentation may encourage other clinicians to perform a thorough examination of the retina through fundoscopy, OCT, and IVFA when evaluating patients with hyperbilirubinemia.

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Brief Summary Statement: A 16-year-old Caucasian male with Gilbert syndrome was found to have retinal pigment epithelium changes, retinal venous anastomoses, and temporal retinal nonperfusion in both eyes. The authors propose a mechanism underlying these changes related to the known role of bilirubin in angiogenesis and as a pro- and anti-oxidant.

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