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Late-onset Stargardt disease

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ABSTRACT

Purpose: To report a case of late-onset Stargardt disease, discuss the differential diagnosis, and review the role of vitamin A supplementation in Stargardt disease.

Observations: A 60-year-old man presented with blurry vision in the right eye for the past two years. Current medications included a daily multivitamin containing vitamin A and age-related eye disease study vitamins. Examination revealed bilateral macular atrophy and scattered yellow flecks which were intensely hyperautofluorescent. Fluorescein angiography revealed a dark choroid. Full-field electroretinogram showed normal rod and cone responses, and genetic testing revealed two pathogenic *ABCA4* gene variations confirming the diagnosis of late-onset Stargardt disease.

Conclusions: Stargardt disease is typically described in young patients but may develop later in adulthood and masquerade as age-related macular degeneration and a number of other conditions. Though the evidence is limited, there is concern that high-dose vitamin A supplementation could lead to progression of Stargardt disease. Avoidance of high-dose vitamin A supplementation should be discussed with Stargardt disease patients.

1. Introduction

Stargardt disease (SD) has an autosomal recessive pattern of inheritance and is associated with *ABCA4* mutations.[1,2] The classic findings in SD are foveal atrophy and yellow-white flecks in the posterior pole.[1] Though typically described in young patients, SD may present later in adulthood and masquerade as age-related macular degeneration (AMD) and a number of other conditions.[2,3] Herein, we report a case of late-onset SD, discuss the differential diagnosis, and review the role of vitamin A supplementation in SD.

2. Case report

A 60-year-old man presented with right eye blurry vision for two years. Medications included age-related eye disease study (AREDS) vitamins and a multivitamin containing vitamin A. Family ocular history included possible macular degeneration in his father. Vision was 20/40 in the right eye and 20/20 in the left eye. Anterior segment examination was unremarkable. Dilated examination revealed scattered subretinal yellow flecks and macular atrophy bilaterally (Fig. 1A and B). The flecks were hyperautofluorescent (Fig. 1C and D). Fluorescein angiography showed obscuration of background choroidal fluorescence and window defects associated with the atrophy (Fig. 1E and F). Optical coherence tomography showed foveal atrophy and hyperreflective deposits at the level of the retinal pigment epithelium (RPE) (Fig. 1H). Full-field electroretinogram showed normal rod and cone responses.

Genetic testing by target enrichment and next-generation sequencing was performed (Molecular Vision Laboratory, Hillsboro, Oregon) and revealed two pathogenic variations in the *ABCA4* gene, c.5461-10T>C[4] and c.5603A>T,[5] confirming the diagnosis of late-onset SD. He was counseled on the condition and the concern that high-dose vitamin A supplementation may lead to progression of SD. He was advised that the original AREDS formulation contained a high dose of beta-carotene, a source of vitamin A, and therefore should be avoided and that other supplements containing vitamin A should be limited as well.

3. Discussion

The differential diagnosis of SD includes AMD; *PRPH2* gene-associated pattern dystrophy; mitochondrial retinal dystrophy associated with maternally inherited diabetes and deafness (MIDD) and occasionally with mitochondrial encephalomyopathy, lactic acidosis, and

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stroke-like episodes; autosomal dominant Stargardt-like macular dystrophy; and pentosan polysulfate toxic maculopathy.[2,3] A number of features can be used to differentiate SD from these other conditions. The drusen of AMD tend to be round and not pisciform, more centered in the macula, less symmetric between the eyes, and less intensely hyperautofluorescent. Pattern dystrophy may have flecks but is typically associated with an autosomal dominant inheritance pattern. Mitochondrial retinal dystrophy may present with RPE deposits and atrophy but is associated with maternal inheritance and, in the case of MIDD, a personal history of diabetes and sensorineural hearing loss. Autosomal dominant Stargardt-like macular dystrophy is associated with *ELOVL4* gene variants and may produce fundus findings similar to SD, but a dominant mode of inheritance would be expected. Pentosan polysulfate maculopathy may present with patterned RPE deposits and macular atrophy, but can be ruled out if the patient has never taken the drug. Angiographic findings of a dark choroid, while common in SD, would not be expected in the other aforementioned diseases.

The *ABCA4* gene encodes a transmembrane protein expressed in photoreceptors that is involved in the transport of retinoids from photoreceptors to the RPE.[1] Dysfunction of the transporter resulting from *ABCA4* mutations leads to the accumulation of lipofuscin deposits in retinal pigment epithelial cells, seen clinically as yellow-white fleck lesions which are intensely hyperautofluorescent.[1,2] Fluorescein angiography typically shows a dark choroid because the buildup of lipofuscin in the retinal pigment epithelium obscures background choroidal fluorescence. The lipofuscin deposits contain the cytotoxic bisretinoid N-retinylidene-N-rethinolamine (A2E), which is believed to contribute to RPE and photoreceptor dysfunction.[6] A2E is derived from the vitamin A conversion product all-trans-retinal which is released following photoexcitation. As a result, there is theoretical concern that vitamin A

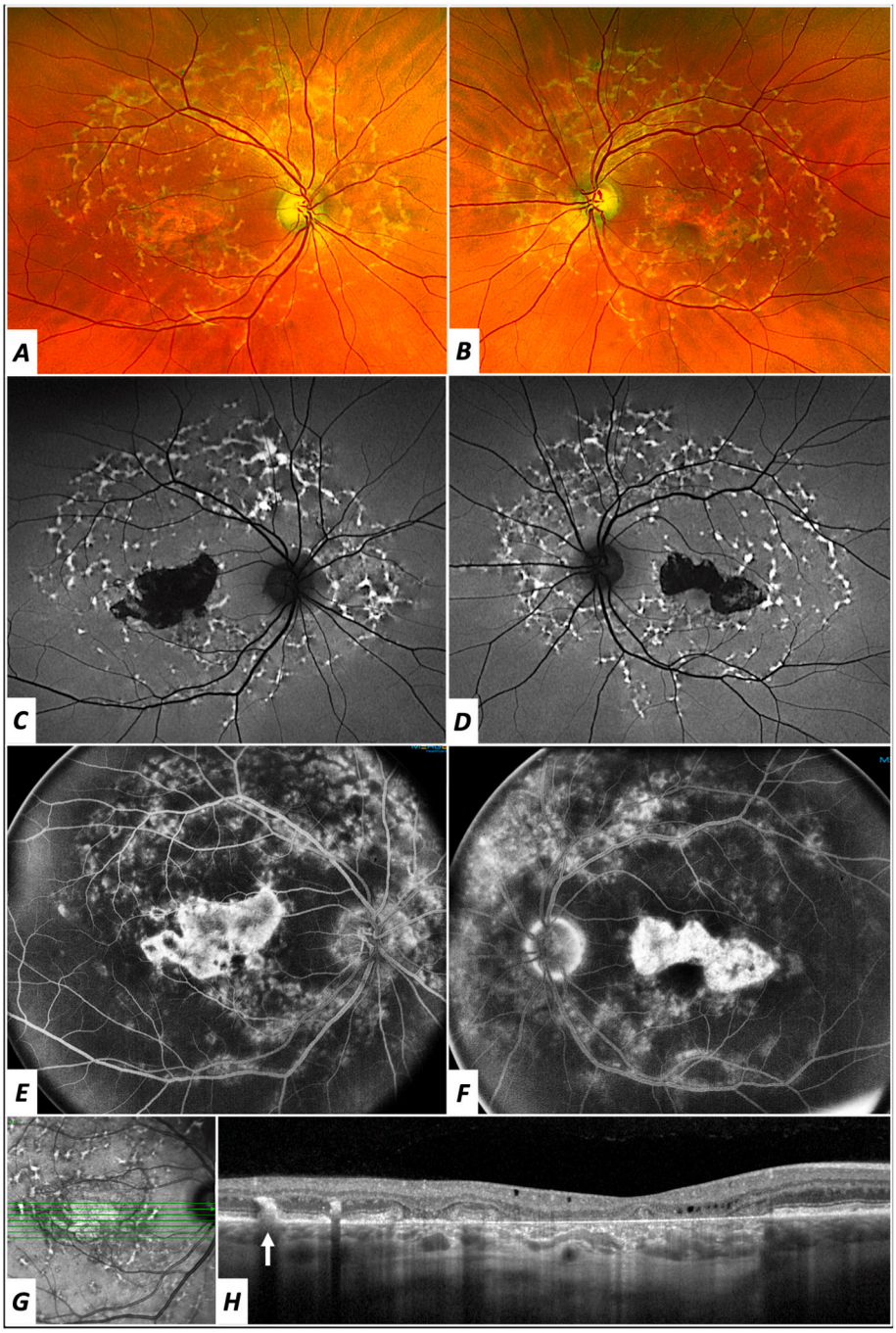

Fig. 1. Fundus photographs (A and B) show scattered yellow flecks in the posterior pole and foveal atrophy. Fundus autofluorescence (C and D) shows hyperautofluorescent flecks and hypoautofluorescence associated with the foveal atrophy. Fluorescein angiography (E and F) shows obscuration of choroidal fluorescence and window defect hyperfluorescence in the central macula due to RPE atrophy and mottled fluorescence associated with the flecks. The flecks are hyperreflective on en face near-infrared reflectance imaging (G). Optical coherence tomography scan (H) shows atrophy of the RPE and outer retina at the fovea. There are hyperreflective deposits at the level of the RPE corresponding to the flecks seen clinically (arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

supplementation could lead to increased lipofuscin accumulation and subsequent progression of SD.

Studies using a mouse model for SD have suggested some support for this hypothesis. Radu and colleagues found that administration of N-(4-hydroxyphenyl)retinamide, an agent that reduces serum vitamin A levels, to *Abca4−/−* knock out mice led to the reduction of A2E accumulation and lipofuscin autofluorescence in the RPE.[7] In a later study, the same group demonstrated increased RPE lipofuscin deposition in *Abca4−/−* mice fed with a vitamin A-supplemented diet compared to those fed a normal diet.[8] The investigators used a murine daily dosage of vitamin A corresponding to a 15,000 IU per day vitamin A dosage for humans.

Federspiel and colleagues reviewed these findings and other investigations in a systematic review of vitamin A in SD and concluded that the evidence to support the role of vitamin A in accelerating SD is both sparse and inconclusive.[6] At the same time, noting the absence of evidence to exclude a role of vitamin A in disease progression, they felt it was prudent to advise patients with SD to limit the use vitamin A supplements. The National Eye Institute currently recommends SD patients avoid "dietary supplements with more than the daily recommended amount of vitamin A".[9] Importantly, complete elimination of dietary vitamin A is not recommended for SD patients given the risk of vitamin A deficiency.[6]

Beta-carotene is a vitamin A precursor that is converted to vitamin A in the intestine, taken up by the liver for storage, and then delivered to the RPE via retinol-binding protein for use in the visual cycle.[10] The original AREDS formulation contains 15 mg per day beta-carotene, the equivalent of 25,000 IU per day vitamin A.[11] It would be prudent, therefore, for SD patients to avoid AREDS vitamins. In contrast, the Age-Related Eye Disease Study 2 (AREDS2) vitamins do not contain beta-carotene, but instead the xanthophyll carotenoids lutein and zeaxanthin.[11] It has been hypothesized that lutein and zeaxanthin could be protective in SD, and lutein supplementation has been shown to augment macular pigment optical density in patients with *ABCA4* disease.[12] Arunkumar and colleagues also recently demonstrated reduced bisretinoid formation following lutein and zeaxanthin supplementation in a mouse model of SD.[13]

4. Conclusions

SD may masquerade as age-related macular degeneration and a number of other conditions. Though the evidence is inconclusive, there is concern that high-dose vitamin A supplementation may lead to progression of SD. The avoidance of excessive vitamin A supplementation should be discussed with SD patients.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to identification of the patient.

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Other disclosures

None.

Authorship

Both authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

Neither of the authors have a proprietary interest in the material presented in this study.

References

1. Tanna P, Strauss RW, Fujinami K, Michaelides M. Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol*. 2017 Jan;101(1):25–30.
2. Westeneng-van Haaften SC, Boon CJ, Cremers FP, et al. Clinical and genetic characteristics of late-onset Stargardt's disease. *Ophthalmology*. 2012 Jun;119(6):1199–1210.
3. Ricca AM, Han IC, Sohn EH. Stargardt disease masquerades. *Curr Opin Ophthalmol*. 2021 May 1;32(3):214–224.
4. Aukrust I, Jansson RW, Bredrup C, et al. The intronic ABCA4 c.5461-10T>C variant, frequently seen in patients with Stargardt disease, causes splice defects and reduced ABCA4 protein level. *Acta Ophthalmol*. 2017 May;95(3):240–246.
5. Zernant J, Lee W, Collison FT, et al. Frequent hypomorphic alleles account for a significant fraction of ABCA4 disease and distinguish it from age-related macular degeneration. *J Med Genet*. 2017 Jun;54(6):404–412.
6. Federspiel CA, Bertelsen M, Kessel L. Vitamin A in Stargardt disease-an evidence-based update. *Ophthalmic Genet*. 2018 Oct;39(5):555–559.
7. Radu RA, Han Y, Bui TV, et al. Reductions in serum vitamin A arrest accumulation of toxic retinal fluorophores: a potential therapy for treatment of lipofuscin-based retinal diseases. *Invest Ophthalmol Vis Sci*. 2005 Dec;46(12):4393–4401.
8. Radu RA, Yuan Q, Hu J, et al. Accelerated accumulation of lipofuscin pigments in the RPE of a mouse model for ABCA4-mediated retinal dystrophies following Vitamin A supplementation. *Invest Ophthalmol Vis Sci*. 2008 Sep;49(9):3821–3829.
9. Stargardt Disease. National eye Institute. Nei.nih.gov, [cited 2022 Jan 27]. Available from: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/stargardt-disease; 2022.
10. Harrison EH. Mechanisms of transport and delivery of vitamin A and carotenoids to the retinal pigment epithelium. *Mol Nutr Food Res*. 2019 Aug;63(15), e1801046.
11. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA*. 2013 May 15;309(19):2005–2015.
12. Aleman TS, Cideciyan AV, Windsor EA, et al. Macular pigment and lutein supplementation in ABCA4-associated retinal degenerations. *Invest Ophthalmol Vis Sci*. 2007 Mar;48(3):1319–1329.
13. Arunkumar R, Gorusupudi A, Li B, et al. Lutein and zeaxanthin reduce A2E and iso-A2E levels and improve visual performance in Abca4$^{-/-}$/Bco2$^{-/-}$ double knockout mice. *Exp Eye Res*. 2021 Aug;209:108680.