Multimodal Imaging Study of Patients With Vitamin A Deficiency Retinopathy

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OBJECTIVES: To describe multimodal imaging findings of vitamin A deficiency retinopathy.

METHODS: A retrospective study of patients with serum retinol < 0.3 mg/L. Fundus color photos, spectral domain-optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF) were reviewed and, when available, electrophysiological tests were analyzed.

RESULTS: Forty-five eyes (63.9 ± 15.7 years) were included. Ultra-widefield fundus photography showed drusen-like deposits (53.3%) and macular retinal pigment epithelium (RPE) mottling (40%). The deposits were hypoautofluorescent, and a perifoveal hyperautofluorescent ring was present in 8.9%. By SD-OCT, the ellipsoid zone had an irregular appearance (100%) and conical deposits anterior to the RPE (33.3%). Electroretinogram (ERG) (66.7%) showed a decrease in b-wave in the scotopic registers, and microperimetry (4.4%) showed decreased foveal sensitivity. After vitamin A supplementation, SD-OCT and FAF showed resolution of all findings. Forty percent of eyes had restoration of the scotopic registers in ERG and improved macular sensitivity by microperimetry (4.4%).

CONCLUSIONS: Vitamin A deficiency causes a mild cone dysfunction in addition to the more severe absent rod response.

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Vitamin A is an essential fat-soluble vitamin that is needed for normal functioning of the visual system,[1] maintenance of cell function, and immunity.[2] Vitamin A deficiency can be secondary to malnutrition, malabsorption due to gastrointestinal surgeries or inflammatory bowel diseases, and tumors. As obesity-related conditions are exponentially growing, and bariatric surgeries are increasingly being performed,[3,4] cases of vitamin A malabsorption syndrome have increased.

In the eye, vitamin A plays a crucial role for phototransduction and visual function. While ocular-related manifestations are rarely described in developed society, vitamin A deficiency is the world's leading preventable cause of childhood blindness.[5] The most common and earliest ocular symptom of vitamin A deficiency is night blindness. In addition, keratomalacia, corneal xerosis, and retinopathy have been described.[6]

Vitamin A deficiency retinopathy can present with granular deposits in the posterior pole or the mid periphery (**Figure 1A**) or can cause a stippled macular appearance[7] with focal retinal pigment epithelium (RPE) changes (**Figure 1B**, **Figure 1C**).[8] Numerous case reports have described the presence of punctuate white spots in the mid-peripheral retina.[9,10] However, no large case series reports the prevalence of different retina manifestations in patients with vitamin A deficiency. This study aims to present the largest cohort of vitamin A deficiency retinopathy examined through ultra-widefield fundus photography (UWF-FP) and spectral domain-optical coherence tomography (SD-OCT). When available, other multimodal imaging modalities will be reviewed as well.

METHODS

This was a retrospective review of patients with clinical evidence of vitamin A deficiency who were referred for ophthalmology consultation. The respective coauthors determined Institutional Review Board approval according to the requirements established

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by their institutional centers. The study complied with the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki.

Patients with a known clinical diagnosis of vitamin A deficiency at each institution based on a plasma or serum retinol concentration < 0.3 mg/L were identified through a retrospective review of the ophthalmology medical records. Inclusion criteria were: (1) ophthalmic involvement based on the clinical history of nyctalopia or vision loss, (2) gradable baseline SD-OCT raster scans through the macula, and (3) high-quality color fundus photographs. Eyes with known diagnoses of dry or wet age-related macular degeneration (AMD) or retinal vascular diseases were excluded.

Clinical data, including age, sex, medical history pertaining to the vitamin A deficiency, color testing with Ishihara's tables, findings on slit-lamp examination, and dilated fundus examination, were collected. Baseline and final follow-up Snellen best-corrected visual acuity (BCVA) were recorded and converted to logarithm of the minimal angle of resolution (LogMAR) values.

De-identified multimodal imaging data from the baseline and post-supplementation examination were collected, reviewed, and independently assessed by two masked retina specialists (FP and EC). In case of disagreement between the two examiners, a senior uveitis specialist (PN) was consulted. Color fundus photography was obtained with a conventional 9-field fundus photography camera (Carl Zeiss Meditec and Topcon TRC-NW8F) or an UWF-FP system (Optos Panoramic 200MA; Optos PLC). SD-OCT (Spectralis HRA OCT; Heidelberg Engineering, or Cirrus HD-OCT 4000, version 5.0; Carl Zeiss Meditec) was performed in each patient at baseline and after vitamin A supplementation. Fundus autofluorescence (FAF) was performed with either a 9-field fluorescein angiography (FA) (Carl Zeiss Meditec; Spectralis HRA+OCT; Heidelberg Engineering) or an ultra-widefield system (Optos Panoramic 200MA; Optos PLC). When available, electrophysiological tests (full-field electroretinogram, ffERG; RETIport-scan, Roland Consult) and microperimetry, dark adaptation (RETIdarkadaptation, Ronald Consult), as well as Goldmann (Octopus 900, Haag Streit Int.) and Humphrey visual field, were collected at baseline and final examination.

STATISTICAL ANALYSIS

Continuous variables were reported as mean, standard deviation (SD), median, and range when appropriate. Categorical variables were reported as percentages. All values were expressed as mean ± SD. All statistical analyses were performed using the open-access R software (R Studio Version 1.1.383, R Project, www.r-project.org).

RESULTS

A total of 45 eyes from 24 patients (10 men, 41.6%) whose age at onset of vitamin A deficiency diagnosis ranged from 40 to 92 years (average 63.9 ± 15.7 years) were included in this study. Three of the 24 patients were monocular because of previous trauma.

Nine patients (37.5%) had a history of bariatric surgery, and nine (37.5%) had previous bowel resections. Six patients (25%) had Crohn's disease, three patients (12.5%) had a history of pancreatitis, and three patients (12.5%) had a history of metastatic neuroendocrine tumors of the small intestine. The mean

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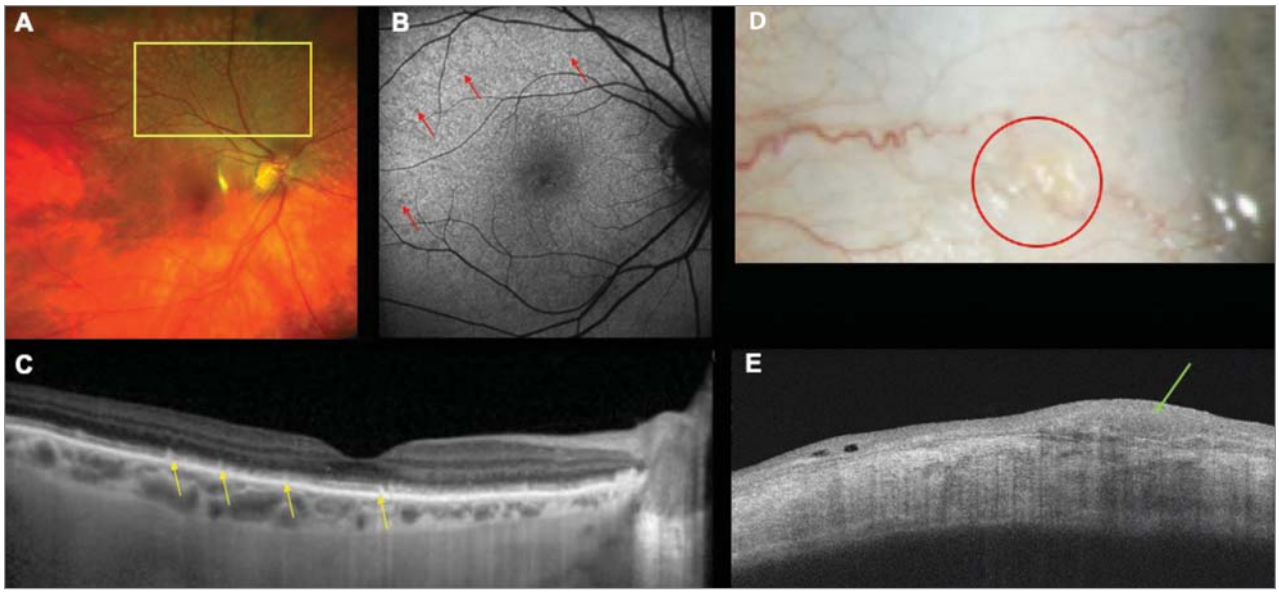

Figure 1. Classic ocular manifestations of one patient with vitamin A deficiency. Subretinal deposits in the central macula or mid periphery (A, yellow square) have been reported in multiple case series; they block the underlying physiological autofluorescence (B, red arrows) and appear on optical coherence tomography as hyperreflective conical lesions above the retinal pigment epithelium (C, yellow arrows). More well-known and easily detectable complications of vitamin A deficiency are Bitot spots (D, red circle), an accumulation of keratin located under the conjunctiva (E, green arrow).

baseline serum vitamin A level was 0.088 ± 0.06 mg/L (range 0.04 to 0.2 mg/L).

The primary reason for ophthalmology referral was nyctalopia (24/24 patients, 100%), followed by altered color perception (12/24 patients, 50%) and severe xerophthalmia (10/24 patients, 41.6%). The mean baseline visual acuity was 0.48 ± 0.89 logMAR (Snellen equivalent: 20/60). Anterior segment examination was unremarkable in 30/45 eyes (66.6%). Severe conjunctival xerosis was found in 7/45 eyes (15.5%), and corneal xerosis in 8/45 eyes (17.7%).

UWF-FP was available for 45/45 (100%); 12/45 eyes (26.7%) also had posterior pole color photography. The presence of intermediate-sized, yellow-white drusen-like deposits (**Figure 1A**, **Figure 3A**) in a mid-peripheral ring pattern was the most common retinal finding (24/45 eyes, 53.3%), followed by macular RPE mottling (18/45 eyes, 40%) (**Figure 2A**, **Figure 2D**). Optic nerve peripapillary atrophy was detected in 8/45 eyes (17.7%), and arteriolar attenuation was present in 6/45 eyes (13.3%).

On fundus autofluorescence (FAF) (available for 21/45 eyes, 46.7%) and FA (15/45 eyes, 33.3%), drusen-like deposits were hypoautofluorescent (**Figure 2B**) and hyperfluorescent in mid-phases, respectively. FAF detected a perifoveal hyperautofluorescent ring in four eyes (8.9%) (**Figure 2B**).

By SD-OCT (available for 45/45 eyes, 100%), inner retinal layers and interfaces were well discriminated. However, the ellipsoid and interdigitation zones were less distinct (**Figure 2C**, **Figure 2G**) and had an irregular appearance in 45/45 eyes (100%). Hyperreflective conical deposits anterior to the RPE were detected in 15/45 eyes (33.3%) at the macular level (**Figure 1C**, **Figure 3C**).

Baseline ffERG was available for 30 eyes (66.7%), disclosing in all eyes a decrease in the amplitude of the b-wave in the scotopic registers with a usual 30-Hz flicker (**Figure 3D**). The dark adaptation was available for one patient and revealed the characteristic absence of the rod-cone break (the so-called Kohlrausch kink).[11]

Microperimetry was available for two eyes (4.4%) at baseline and showed an average perifoveal sensitivity of < 15 dB in both eyes (**Figure 2E**), considerably reduced compared to normal reported values (> 29 dB), with a large central scotoma in the corresponding 24-2 Humphrey visual field. The Goldmann visual field available for one patient showed severe constriction of the I2e and I3e isopter in both eyes and a mild constriction of the III4e isopter in the right eye.

VITAMIN A SUPPLEMENTATION AND PATTERN OF RECOVERY

All patients received oral or intravenous supplementation of vitamin A. The preferred regimen[12] was 100,000 IU/day for 3 days, followed by 50,000 IU/day

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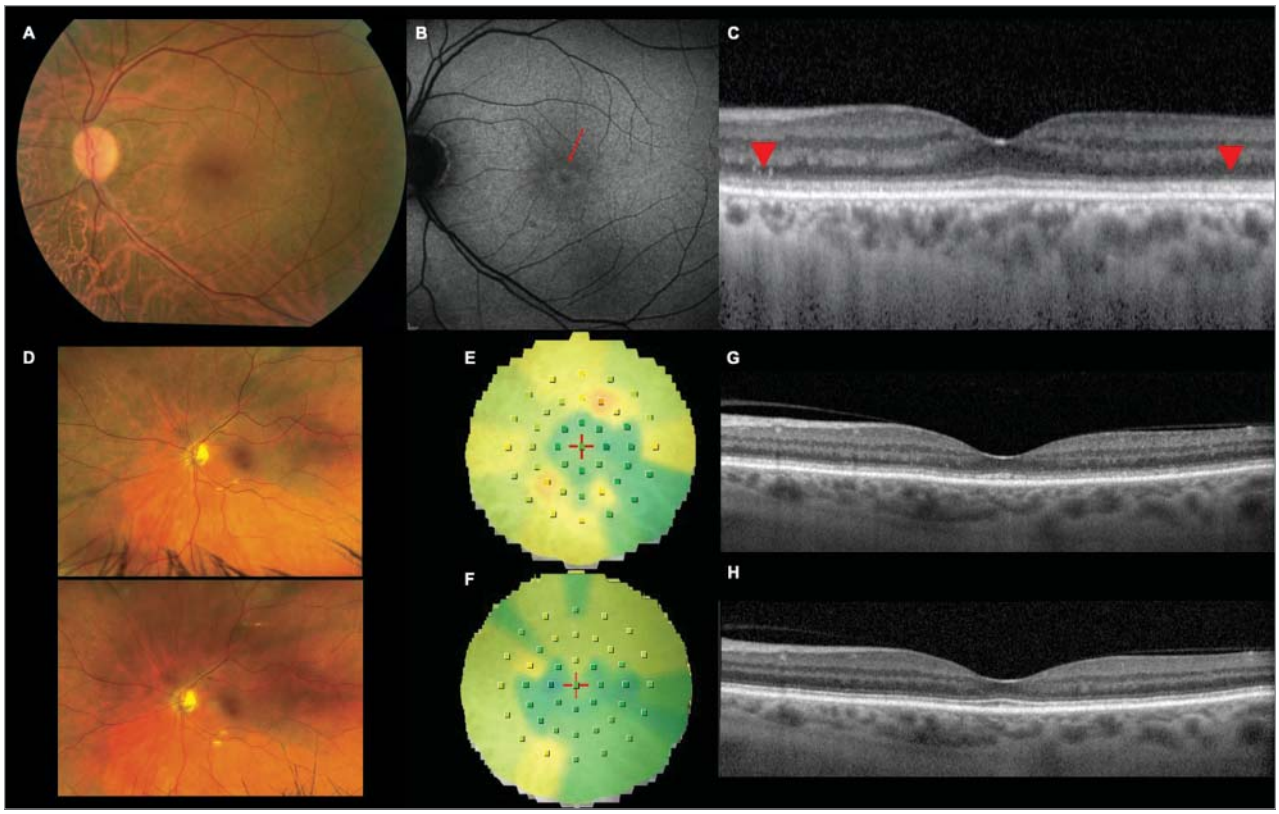

Figure 2. Two cases of cone damage secondary to Vitamin A deficiency. The case portrayed in the superior panel has an unremarkable macular appearance on fundus photo (A) but fundus autofluorescence shows an hyperautofluorescent perifoveal ring (B, red arrow) probably secondary to an increased visualization of the underlying normal retinal pigment epithelium autofluorescence. Spectral domain-optical coherence tomography (SD-OCT) (C) shows a foveal and perifoveal attenuation of the ellipsoid band, compatible with minor damage to the foveal cones. The inferior panel case has, once more, a normal macular appearance on color photo (D) but the baseline microperimetry showed a significant reduction in foveal and perifoveal sensitivity (E) accompanied by fuzziness of the ellipsoid zone on OCT (G). With vitamin A oral supplementation, the cone sensitivity increased on microperimetry (F) and the photoreceptor layer normalized on OCT (H).

for 2 weeks (16/24 patients, 66.7%). Five patients (20.8%) were started on 50,000 IU/day immediately with no loading dose. Two patients (8.3%) received a dose of 30,000 IU/day accompanied by beta-carotene supplementation and one patient (4.2%) received intravenous vitamin A supplementation because of noncompliance with oral treatment.

At the final follow-up (average follow-up time 4.8 ± 2.7 months), mean visual acuity was 0.12 ± 0.1 LogMAR (Snellen equivalent: 20/25). Nyctalopia had resolved in 19 patients (79.2%). SD-OCT was available for all 45 eyes at the final follow-up and showed resolution of the ellipsoid attenuation (**Figure 2H**) with perfect discrimination of the outer bands in 100% of cases and resolution of the hyperreflective subretinal deposits (**Figure 3G**) in 15/15 eyes (100%). Follow-up FAF was available for 10/45 eyes (22.2%) and showed resolution of the hypoautofluorescent dots in all cases (**Figure 3F**), with no legacy on the surrounding retinal signal. Eighteen eyes (40%) showed complete restoration of the scotopic registers in the available follow-up ffERG (**Figure 3H**). At 3 months, in 2/45 eyes (4.4%), microperimetry values of retinal sensitivity greatly improved (> 20 dB), but average macular sensitivity did not reach normal values (**Figure 2F**). Dark adaptation returned to normal 5 months after the start of vitamin A supplementation in one patient.

DISCUSSION

In this study, we summarize the clinical features and the imaging characteristics of patients with laboratory-confirmed vitamin A deficiency in a large, multicentric study. We found that 75% of the cases were secondary to gastrointestinal surgery. The most common findings were yellow-white drusen-like deposits in the mid periphery and RPE mottling in the macula. The macular changes corresponded to the ellipsoid zone and the interdigitation zone on OCT, which completely regressed on follow-up. Despite the small

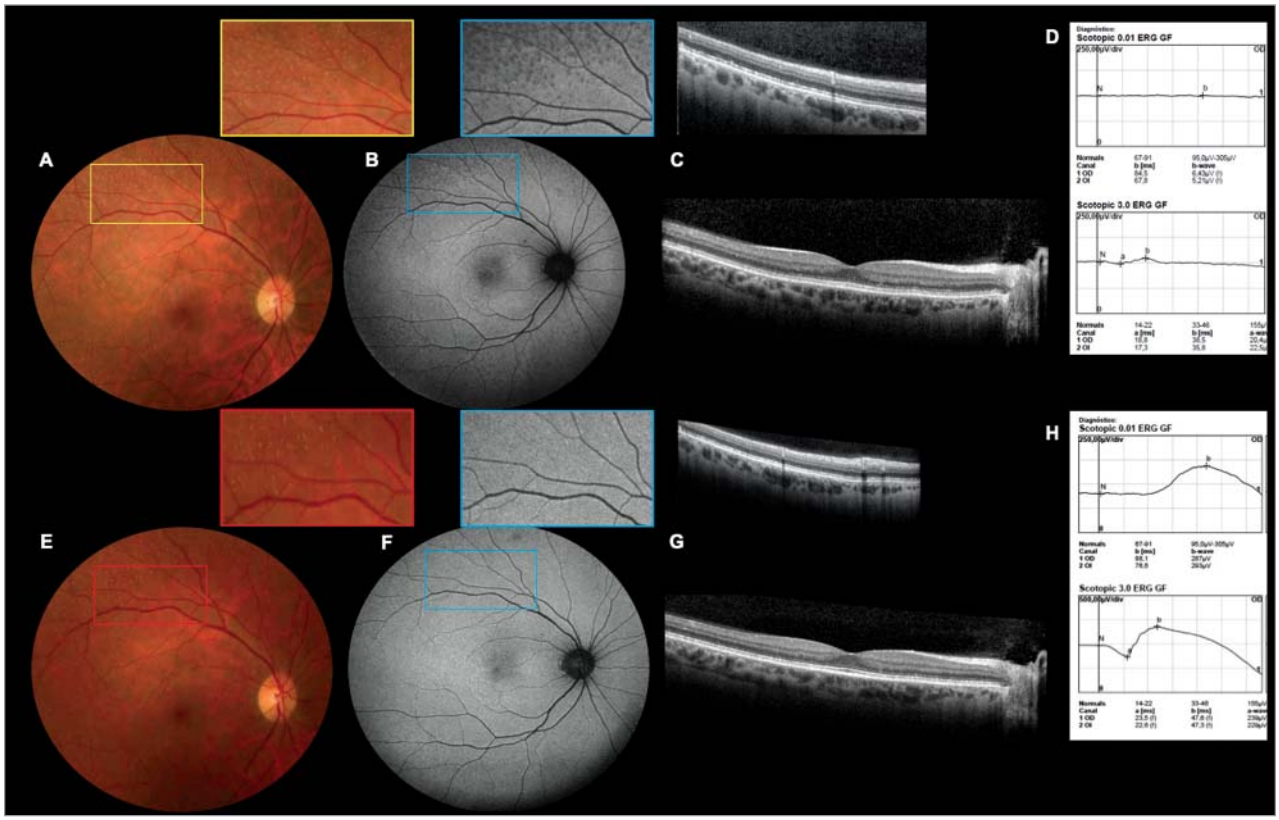

Figure 3. A case of classical rod dysfunction secondary to vitamin A deficiency. The baseline fundus appearance (A) shows yellow retinal deposits along the arcades (yellow rectangle) that block the underlying autofluorescence, thus appearing hypoautofluorescent (B, blue rectangle). These subretinal deposits are sparing the macula on optical coherence tomography (OCT) (C) but can be detected along the superior arcade through a peripheral scan as hyprreflective conical lesions between the retinal pigment epithelium and the retina. Rods dysfunction is confirmed by full field electroretinography (D) showing a decrease in the amplitude of the b-wave in the scotopic registers. After oral vitamin A supplementation, the deposits resolve both in color photo (E) and in autofluorescence (F), not leaving any outer retina change on OCT (G). This is accompanied by a complete restoration of the scotopic registers of full field electroretinography (H).

numbers, functional tests showed a reversible reduction in both central and peripheral sensitivity.

While primary vitamin A deficiency has disappeared in relatively wealthy populations,[13] the higher prevalence of obesity in wealthier countries[3] has increased the iatrogenic malabsorption syndromes and vitamin A deficiency due to bariatric surgery. Patients with chronic pancreatitis[14] and inflammatory bowel disease[15] are also at risk for developing vitamin A deficiency. Mammals cannot synthesize retinol[1,2] and thus depend on intestinal absorption of this micronutrient as preformed dietary vitamin A (retinyl esters and retinol) or as the precursor beta-carotene.

Vitamin A deficiency is estimated to be responsible for about half a million cases of irreversible blindness each year. Vitamin A deficiency is perhaps most striking when it manifests as night blindness[16] (delayed dark adaptation). This deficit reflects an insufficient supply of 11-cis-retinaldehyde, the vitamin A-derived chromophore of visual pigment in rods and cones. In the current case series of 45 eyes with vitamin A deficiency retinopathy, the most common symptom was nyctalopia (100% of patients) that largely resolved after vitamin supplementation therapy.

The clinical, extraretinal manifestations of vitamin A deficiency, including Bitot spots and xerosis,[6,17,18] are widely known and can be identified readily on slit-lamp examination. However, there is limited information on the fundus findings and their response to vitamin A therapy. Despite the advent of newer retinal imaging techniques that give a more in-depth view of retinal anatomy, only six case reports[7-10,19] in the past 10 years have studied the retinal findings associated with vitamin A deficiency. Therefore, our study aims to present the multimodal retinal imaging findings of a large cohort of patients with vitamin A deficiency.

While vitamin A deficiency is typically thought to clinically impact rod function,[20] the decreased color

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vision and reduced visual acuity present in our series (50% and 100%, respectively) seem to indicate an additional but milder cone dysfunction.[21] This theory is supported by the irregular appearance of the interdigitating zone and inner-outer segment junction that was present in our series in 100% of baseline foveal scans. In addition, FAF of four eyes showed an hyperautofluorescent perifoveal ring that may represent an accelerated lipofuscin synthetic pathway initiated in disabled cones cells unable to detoxify excess retinaldehyde of the visual cycle. One of our patients had baseline microperimetry showing poor macular sensitivity, paralleled by large scotomata in the central vision on Humphrey visual field. Following treatment with vitamin A, microperimetry values improved significantly with the important recovery of central vision. All these findings indicate a transitory and mild damage to the cone system secondary to vitamin A deficiency, less severe compared to rod system damage.

Rods are disproportionately more affected than cones in cases of vitamin A deficiency,[20] as demonstrated by the absent rod response on ffERG (66.7%) with only mildly decreased amplitude or increased implicit time of the cone response. Rods consume a high amount of energy to maintain a continuous depolarized state in darkness.[20] This fact may explain why they are affected more than cones in certain nutritional disorders, including vitamin A deficiency. The rods' reaction to vitamin A deficiency seems to manifest clinically with midperipheral retinal white/yellow dots that co-localize to subretinal hyperreflective deposits on SD-OCT. These deposits are generally preferentially found in the superior macula. This area corresponds to the region of the highest density of rods in the human retina.[22] Aleman et al.[19] and Nishida et al.[23] in 2013 were the first to simultaneously report two cases with these structural changes on SD-OCT in vitamin A deficiency. We identified these extramacular white dots in 53.3% of eyes on fundus photography, and on SD-OCT the hyperreflective cones that accumulated beneath the ellipsoid band replacing the photoreceptor outer segment signal were present in 33.3% of eyes. The corresponding fundus hypoautofluorescence observed could represent a localized loss of lipofuscin[24] due to the lack of one of its precursors, vitamin A, or screening of the RPE fluorescence by the material originating from the disrupted outer segments.[19] Alternatively, a decrease in the emittance due to a blockage effect of the subretinal deposits may be an explanation. It has been suggested that the white lesions correspond to disruption and accumulation of shed photoreceptor outer segment above the RPE, similar to subretinal drusenoid deposits (SDDs) described as part of the AMD spectrum. Consistently, characteristic SDDs usually present hypoautofluorescence on FAF.

Electrophysiological changes in vitamin A deficiency and the reversal of such changes following treatment have mainly been reported.[25,26] As such, the ffERG changes in the scotopic register that were registered in 66.7% of our patients and their resolution (40%) mirror what has been previously published.

The conclusions we may draw from the present study are limited by its retrospective and uncontrolled methodology and the limited number of individuals studied. A referral bias likely exists in this study because patients seen in tertiary care centers included in this study are followed more closely than the general population, and the severity of the underlying vitamin A deficiency is likely to be associated with a higher frequency and severity of retinal changes. The results reported might have been less strong had a general population sample been available. Still, it is not very likely that the pattern of response to treatment would have been qualitatively different.

Furthermore, given the inclusion criteria of patients with ocular symptoms, our results are likely biased toward positive multimodal imaging findings, and the prevalence of these findings may be low overall for patients with vitamin A deficiency without eye symptoms.

Additionally, even if we excluded all patients with a known diagnosis of AMD, we cannot be sure to have SDDs secondary to a newly diagnosed AMD. While this seems unlikely, considering the universal resolution of the deposits with vitamin A supplementation, this limitation must be acknowledged.

Finally, using data from both eyes of the same person that was taken into analysis in this study can lead to bias. There was intrinsic similarity in the retinal features between the two eyes of the same person, but the clinical characteristics could be very different from the others.

CONCLUSION

We report the largest case series of retinal changes secondary to vitamin A deficiency, analyzed and followed through multimodal imaging. Our results confirm the primary involvement of the rod system that has been previously reported in the literature; in addition, multimodal imaging shows a minor and partial involvement of the foveal and perifoveal cones which needs to be more widely recognized. A prompt diagnosis of vitamin A deficiency retinopathy is paramount, as the clinical and imaging findings we described are reversible through timely dietary supplementation.

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