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CLINICAL CASE REPORT

Retinal structure in vitamin A deficiency as explored with multimodal imaging

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Abstract
Purpose To define the retinal structural abnormalities in a patient with vitamin A deficiency.
Methods The patient had a complete ophthalmic examination, electroretinography (ERG), short-wave fundus autofluorescence (SW-AF) and spectral domain optical coherence tomography (SD-OCT) imaging. Serum vitamin A levels were measured.
Results A 63-year-old man with alcoholic cirrhosis, sclerosing cholangitis and chronic pancreatitis experienced blurred vision and nyctalopia for over a year. There was no family history of eye disorders or consanguinity. His best-corrected visual acuity was 20/20 in each eye; color vision as determined with Ishihara color plates was normal in each eye. Anterior segment examination was unremarkable. He was pseudophakic in both eyes. Standard ERGs showed non-detectable rod function, a cone-mediated dark-adapted response to the standard flash and borderline reduced cone function. Serum vitamin A levels were below 0.06 mg/L (normal 0.3–1.2 mg/L). Fundus examination revealed numerous round yellow–white lesions along the superior arcade and nasal to the optic nerve in both eyes. These lesions were hypoautofluorescent on SW-AF. SD-OCT cross sections demonstrated that they were focal disruptions distal to the ellipsoid band of the photoreceptors with hyperreflective images bulging up the ellipsoid and region. The retinal pigment epithelium and the inner retina appeared intact. Limited and gradual vitamin A supplementation for over a month (20 000 IU/day) led to a dramatic improvement in retinal function and to the resolution of the symptoms. The retinal lesions remained unchanged.
Conclusions Imaging of this patient with nyctalopia and severe rod dysfunction suggests that the retinal white lesions known to occur in vitamin A deficiency localize to the photoreceptor layer, particularly the outer segment. On OCT, they are reminiscent of lesions observed in genetic diseases with retinoid cycle dysfunction and of drusenoid subretinal deposits, an abnormality commonly associated with age-related macular degeneration.

Keywords Vitamin A · Optical coherence tomography · Photoreceptors · Rods · Retinoid cycle

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Introduction

Vitamin A is essential for normal retinal function [1]. Prolonged malnutrition, malabsorption or abnormal vitamin A metabolism can lead to vitamin A deficiency and to visual symptoms. Night blindness is one of the earliest manifestations of this condition, a consequence of reduced rhodopsin levels, rod sensitivity loss and

slowed dark adaptation [2–4]. In this work, we use multiple imaging modalities and electroretinography to explore in detail the structural and functional abnormalities of a patient with vitamin A deficiency. The structural changes observed in our patient are compared with those reported in diseases in which mutations in different genes lead to abnormalities in the retinal retinoid (vitamin A) cycle.

Case report

A 63-year-old man with alcoholic cirrhosis, sclerosing cholangitis and chronic pancreatitis diagnosed over 5 years earlier had been experiencing blurred vision and nyctalopia for a year. The patient had a history of occasional diarrhea in the past. There was no family history of eye disorders or consanguinity. Best-corrected visual acuity was 20/20 in each eye. Color vision as determined with Ishihara color plates was normal in each eye. Anterior segment examination was unremarkable; he was pseudophakic in both eyes. A full-field standard electroretinogram (ERG) (Espion, Diagnosys LLC, Littleton, MA, USA) showed non-detectable rod function, a cone-mediated dark-adapted response to the standard flash and borderline reduced cone function (Fig. 1). Serum vitamin A levels were below 0.06 mg/L (normal 0.3–1.2 mg/L). Supplementation with oral vitamin A for a month led to improved rod functioning (Fig. 1), although serum vitamin A levels remained at trace levels. Supplementation was limited and gradual (20 000 IU/day) due to patient's concerns regarding the possibility of aggravating his liver dysfunction. Anterior segment examination was normal. Fundus examination revealed numerous yellow–white lesions above the superior vascular arcade and nasal to the optic nerve (Fig. 2a), which colocalized with hypoautofluorescent round lesions on short-wave autofluorescence imaging (SW-AF) (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) (Fig. 2a). Spectral domain optical coherence tomography (SD-OCT) cross sections demonstrated multiple regions of focal disruption of the photoreceptor (PR) outer segments (OS) colocalizing with the hypoautofluorescent lesions. Magnified SD-OCT cross sections demonstrated that neighboring retina could be normal (Fig. 2b, "*a*"). Within the white lesions, there was replacement of the photoreceptor outer segment signal by hyperreflective images that bulge up an otherwise intact overlying ellipsoid band; the underlying RPE layer appears intact (Fig. 2b, "*b*"). In the proximity of some of the lesions, the ellipsoid region (band #2) and the retinal pigment epithelium (RPE) band #4 appeared to be closer together compared to the normal lamination, possibly reflecting shortened OS (Fig. 1d, "*c*"). The outer nuclear layer (ONL) retina overlying this lesion was slightly thinner. The inner retina and the RPE layer were intact.

Discussion

In vivo retinal imaging of this patient with vitamin A deficiency, nyctalopia and profound rod dysfunction

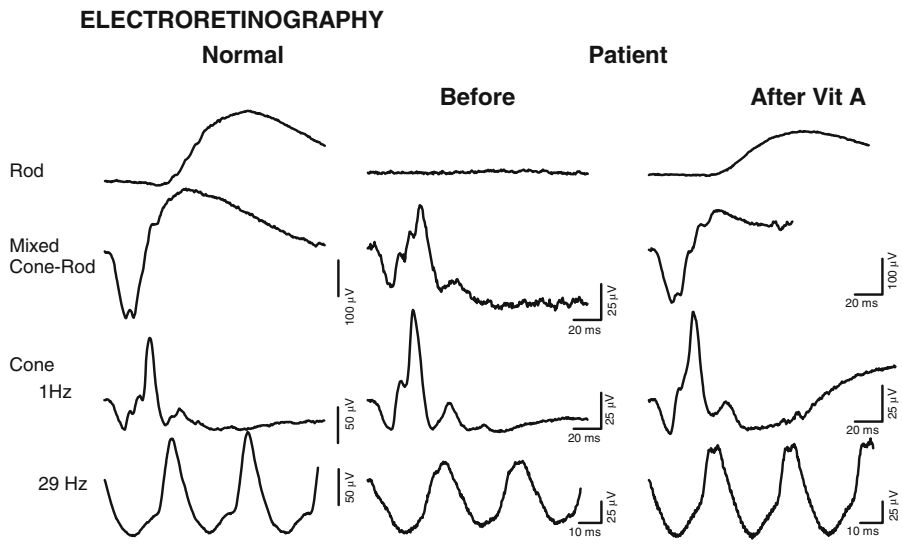

Fig. 1 Retinal function and structure in vitamin A deficiency. **a** Standard ERG [33] (Espion, Diagnosys LLC, Littleton, MA) in the left eye of the patient before (*center column*) and after (*right column*) supplementation with vitamin A, compared to an age-matched normal subject (*left column*)

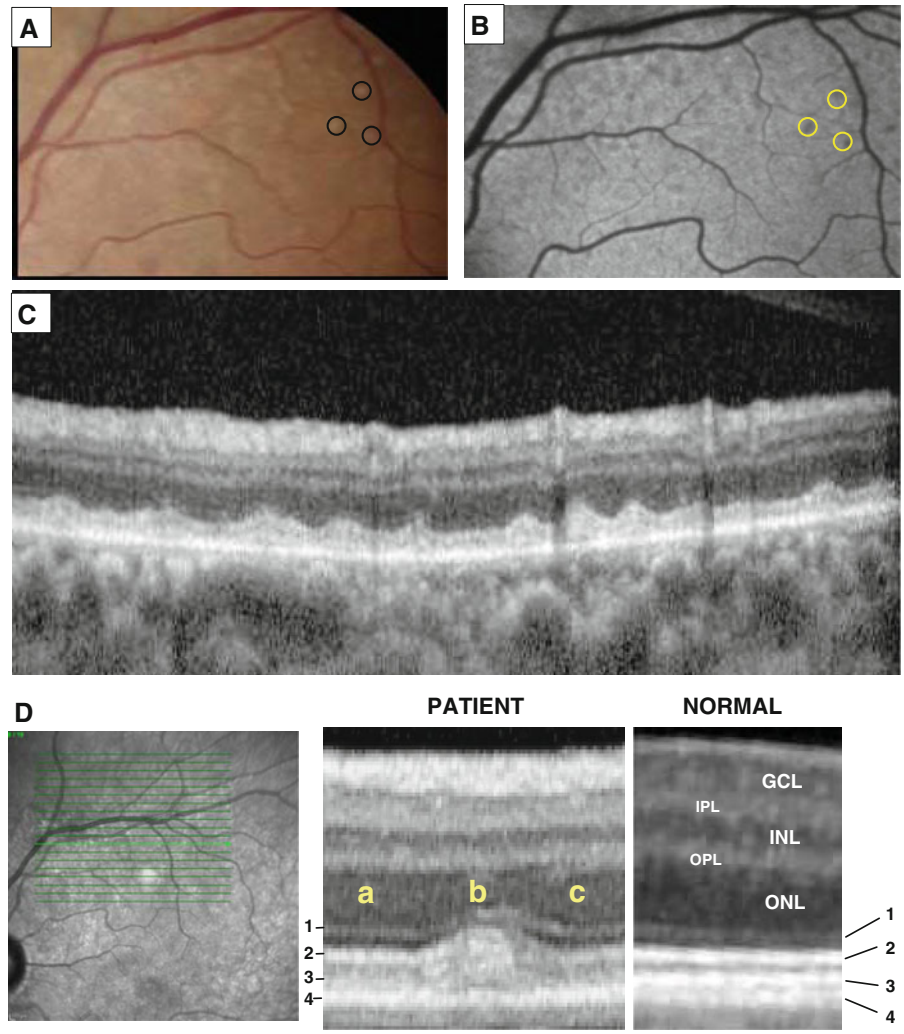

Fig. 2 **a** Fundus image of the left eye showing *white dots* superiorly; right eye showed similar findings (not shown). **b** Short-wave (SW) fundus autofluorescence imaging and SD-OCT (**c**, **d**) (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany) in area of *white dots* depicted in (**a**). Examples of hypoautofluorescent dots that colocalize with fundus *white dots* are *circled* (**a**, **b**). **c** Unstraightened, 8.7-mm-long, SD-OCT cross section from a horizontal raster scan. Thicker *green line* depicted in the infrared image in (**d**) showing multiple areas of outer retinal abnormalities colocalizing with the *white dots* shown in **a** and **b**. **d** Infrared reflectance image from OCT system screen with overlaid horizontal raster scans (*left*) and magnified OCT cross section through one of the *white dots* (*middle panel*) compared to a normal subject (*right panel*). *Retinal layers are labeled*: outer nuclear layer = ONL, inner nuclear layer = INL, gangion cell layer = GCL, IPL, outer plexiform layer = OPL and retinal nerve fiber layer = RNFL. Outer retinal lamination follows nomenclature recently proposed [34]. The outer retina in regions that colocalize with the *white dots* shows a broad hyperreflective image at the level of the photoreceptor outer segments that bulges up the ellipsoid region (labeled "*b*"). The outer retina adjacent to this lesion could be within normal limits ("*a*") or shows a narrowed space between bands *#2* and *#4* ("*c*")

suggests that the white lesions observed in our patient correspond to disruptions and possible accumulation of shed PR-OS above the RPE and seem to correspond to histologic abnormalities observed in animal models of vitamin A deficiency [5–9]. White-dotted fundus appearance in patients with vitamin A deficiency is a well-recognized feature of this condition [10–12]. OCT changes in the outer retina in association with such lesions have been reported [13]. A white-dotted appearance is also known to occur in a number of retinopathies caused by mutations in genes that encode proteins involved in the retinal retinoid cycle [14–24].

A remarkably similar OCT appearance to the one observed in our patient has been reported in many of these conditions [18, 21–24]. Interestingly, the lesions, whether caused from genetic mutations and abnormalities of the visual cycle or by nutritional deficiency, resemble the OCT appearance of subretinal drusenoid deposits described in AMD and in retinas from older individuals [25, 26]. Of course, the coexistence of subretinal drusenoid deposits with vitamin A deficiency lesions is a possibility.

Photoreceptor outer segment abnormalities and reduction in the phagocytic content of the RPE are known to occur in vitamin A-deficient states induced experimentally and are likely recreated in our patient [2, 27–31]. The localized fundus hypoautofluorescence observed could represent localized loss of lipofuscin 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 [2, 17, 27–31]. Outer retinal abnormalities shared by vitamin A deficiency and by genetic abnormalities of the visual cycle may point to an alternative mechanism causing this OCT abnormality. Interestingly, abnormal availability of vitamin A metabolites to the photoreceptors has been implicated in Sorsby's fundus dystrophy and late-onset retinal degeneration (L-ORD), both genetic maculopathies with photoreceptor dysfunction, dark-adaptation delays and white-dotted retinal appearance that are responsive to vitamin A supplementation [4, 32]. Our findings support the notion that a localized retinoid-deficient state at the photoreceptor level resulting from reduced vitamin A bioavailability or by a genetically determined retinoid cycle defect leads to photoreceptor outer segment changes. It is also possible that some age-related retinal changes with white-dotted appearance on fundus examination may share features of this physiopathology.

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Conflict of interest None.

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