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CLINICAL CASE REPORT

Vitamin A deficiency after prolonged intake of an unbalanced diet in a Japanese hemodialysis patient

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Abstract

Background In industrialized countries, vitamin A deficiency (VAD) is extremely rare, except association with bariatric surgeries and hepatobiliary disorders. It is unusual that VAD develops during hemodialysis due to reduced glomerular filtration of vitamin A-binding protein. We reported the case of a 58-year-old Japanese male hemodialysis patient diagnosed with VAD.

Case presentation The patient undergoing hemodialysis for more than 15 years presented with progressive photophobia and night blindness and was ophthalmologically examined. He denied a history of cancer or hepatobiliary disease and reported that he loved eating prepackaged noodle bowls and foods, with prolonged low intake of fruits/vegetables. He had good visual acuity. Fundus images showed numerous white dots in the midperipheral retinae, but no degenerative changes. In baseline full-field electroretinography (ERG), b-wave responses were extremely reduced in rod ERG, a-wave amplitudes in standard-flash/strong-flash ERG were reduced to 20–25% of our controls, a- and b-wave amplitudes in cone ERG were reduced to 40–50% of the controls. Whole-exome sequencing identified no pathogenic variant for any inherited retinal disorder. He was diagnosed with VAD because of reduced serum vitamin A levels and treated with retinol palmitate. Two months after treatment commencement, the serum vitamin A level was within the normal range. Full-field ERG showed that the scotopic ERG responses markedly improved compared with baseline.

Conclusions This is the first report of VAD associated with undernutrition in the Japanese hemodialysis population.

Keywords Retina · Electroretinography · Renal failure · Undernutrition · Fat-soluble vitamin · Whole exome sequencing

Introduction

In developing countries, vitamin A deficiency (VAD) associated with malnourishment is a major cause of blindness [1]. In industrialized countries, however, VAD is extremely rare, except in patients with histories of malabsorptive bariatric surgeries, hepatobiliary disorders, or pancreatic diseases [2–4]. VAD can lead to a variety of ocular disorders, ranging from night blindness to xerophthalmia [1, 5].

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Retinol, which is bound to retinol-binding protein 4 (RBP4), is the major clinically relevant form of vitamin A found in the circulation. Vitamin A and retinol levels have been shown to be elevated in patients undergoing hemo- or peritoneal dialysis [6] due to increased RBP4 levels caused by reduced glomerular filtration [7]. Thus, hemodialysis may protect patients from development of VAD. As far as we investigated, there has been no report of VAD associated with undernutrition in any hemodialysis Japanese patient.

Here, we report a rare case of a Japanese patient undergoing hemodialysis who was diagnosed with VAD due to prolonged intake of an unbalanced diet.

Ethics statement

This case report was approved by the Ethics Committee of The Jikei University School of Medicine (approval numbers: 24–231 6997 and 32–293 10,375). This report adhered to the tenets of the Declaration of Helsinki, and written informed consent was obtained from the patient.

Case presentation

A 58-year-old single male presented with progressive photophobia and night blindness, which had first developed in his 40 s. He had a history of bilateral cataract surgeries at 55 years of age and idiopathic renal insufficiency, for which he had been managed with hemodialysis for more than 15 years. He denied a history of cancer, digestive disorders, or hepatobiliary/pancreatic diseases. He also denied a family history of ocular genetic disorders. He reported that he loved eating prepackaged noodle soups/bowls and other packaged foods, with prolonged low intake of fruits and vegetables.

On examination, his best-corrected visual acuity was 20/16 in both eyes (OU), with an unremarkable slit-lamp examination, except for bilateral pseudophakia. Ultra-wide-field pseudo-color fundus images (Optos California, Optos PLC, Dunfermline, UK) revealed numerous white dots in the midperipheral retinae of both eyes (Fig. 1a, b). Ultra-wide-field fundus autofluorescence images (Optos California) did not demonstrate attenuated retinal vessels nor degenerative changes (Fig. 1c). Horizontal cross-sectional retinal images using optical coherence tomography (Cirrus HD-OCT 5000; Carl Zeiss Meditec, Dublin, CA, USA) showed preserved laminar structures and ellipsoid zones in both maculae (Fig. 1d).

Full-field electroretinography (ERG) was then performed based on the International Society for Clinical Electrophysiology of Vision standard [8], using a light-emitting diode, built-in electrode ERG system (LE-4000, TOMEY, Nagoya, Japan). For strong-flash electroretinography, we used dark-adapted (DA) 200 cd s/m^2 (DA 200) instead of DA 10.0. The procedure and conditions have been previously reported [9–12]. All electroretinographic responses of the patient were compared with those of previously reported controls (n = 23) [12]. In preparation, the right eye (OD) was dark adapted for 24 h, and the left eye (OS) was dark adapted for 30 min, which were performed to exclude inherited retinal disorders (IRDs) with delayed dark adaptation. The patient wore a thick patch over the right eye the day before ERG recordings. On baseline ERG testing (Fig. 2), rod (DA 0.01) ERG showed remaining residual b-wave amplitudes in OD due to the prolonged dark adaptation and extinguished b-wave response in OS. Standard-flash (DA 3.0)/DA 200 ERG demonstrated a-wave amplitudes that were reduced to approximately 20–25% of the controls, with more significant reductions in b-wave amplitudes of DA 200 ERG. Light-adapted (LA) cone (LA 3.0) ERG demonstrated a- and b-wave amplitudes that were reduced to 40–50% of the controls. Amplitudes were reduced to approximately 70% of the controls on LA 30-Hz flicker ERG.

We then conducted a molecular genetic analysis using the patient's blood sample (JU1833) and whole-exome sequencing (WES) (Macrogen, Tokyo, Japan) to identify possible pathogenic gene variant(s) for IRDs such as fundus albipunctatus (OMIM #136,880) and retinitis punctata albescens (OMIM #136,880)/Bothnia retinal dystrophy (OMIM #607,475). Additional blood sample was not available from his family members. The details of the WES methodology have been previously reported [10, 13, 14]. Among 271 IRD genes listed in the Retinal Information Network database (https://sph.uth.edu/retnet/), we searched rare variants (allele frequency < 0.001) of any ethnic subgroup found in the following database, 1000 Genomes database (https://www.

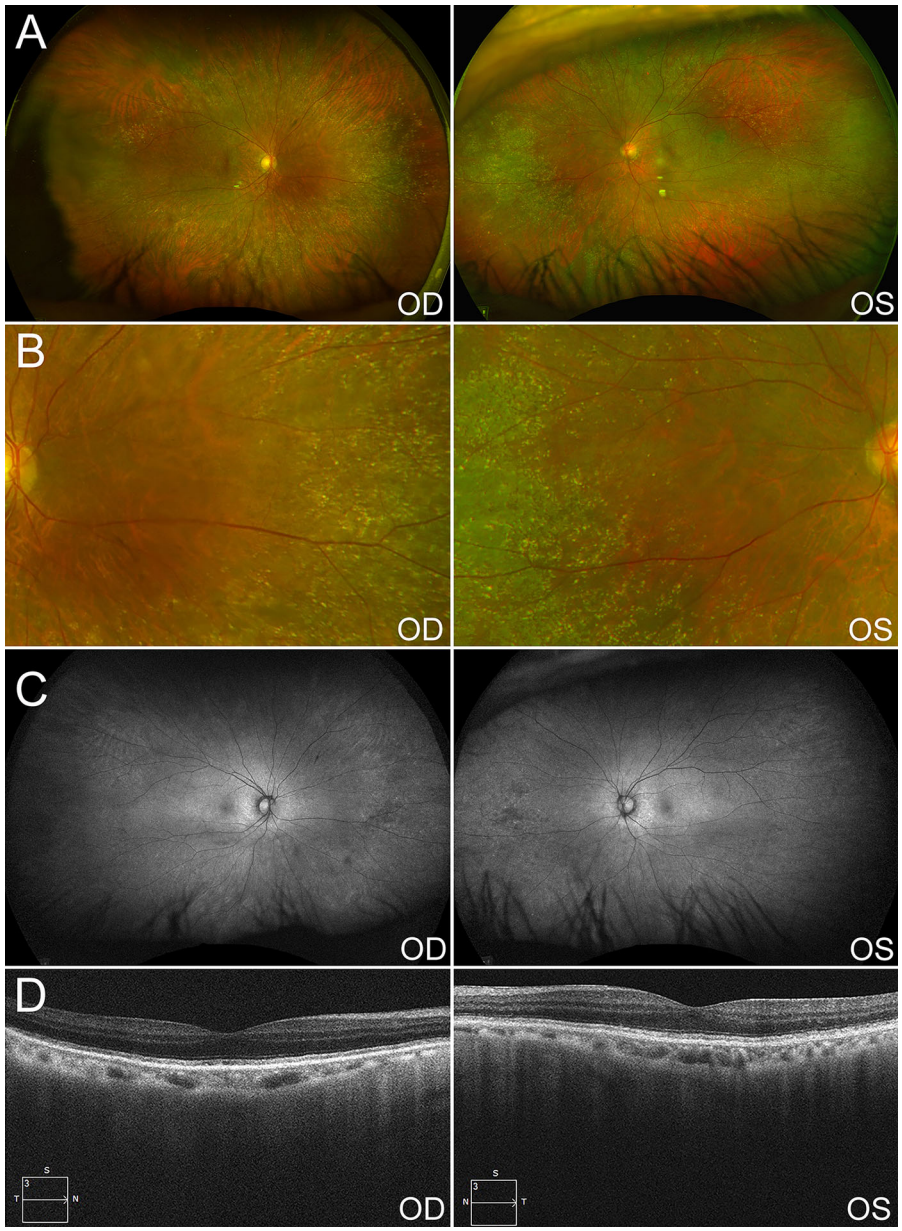

Fig. 1 Multimodal retinal images at patient presentation. **a** Ultra-wide-field fundus images, **b** magnified images of the nasal area, **c** ultra-wide-field fundus autofluorescence images, and **d** optical coherence tomography images of the macula

internationalgenome.org/), Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org/) and Human Genetic Variation Database (http://www.genome.med.kyoto-u.ac.jp/SnpDB/). Consequently, we did not identify any rare heterozygous or homozygous variant in those genes including the *RDH5*, *RPE65*, *LRAT*, *RLBP1*, *RHO*, and *RPPH2* genes, which are responsible for fundus albipunctatus and retinitis punctata albescens [10, 15–17].

Blood testing, however, demonstrated a reduced serum vitamin A level of 76 IU/dl (normal range: 97–316 IU/dl), and the patient was subsequently diagnosed with VAD. His serum zinc and low-density-lipoprotein (LDL) cholesterol levels were 87 μg/dl (normal range: 80 − 130 μg/dl) and

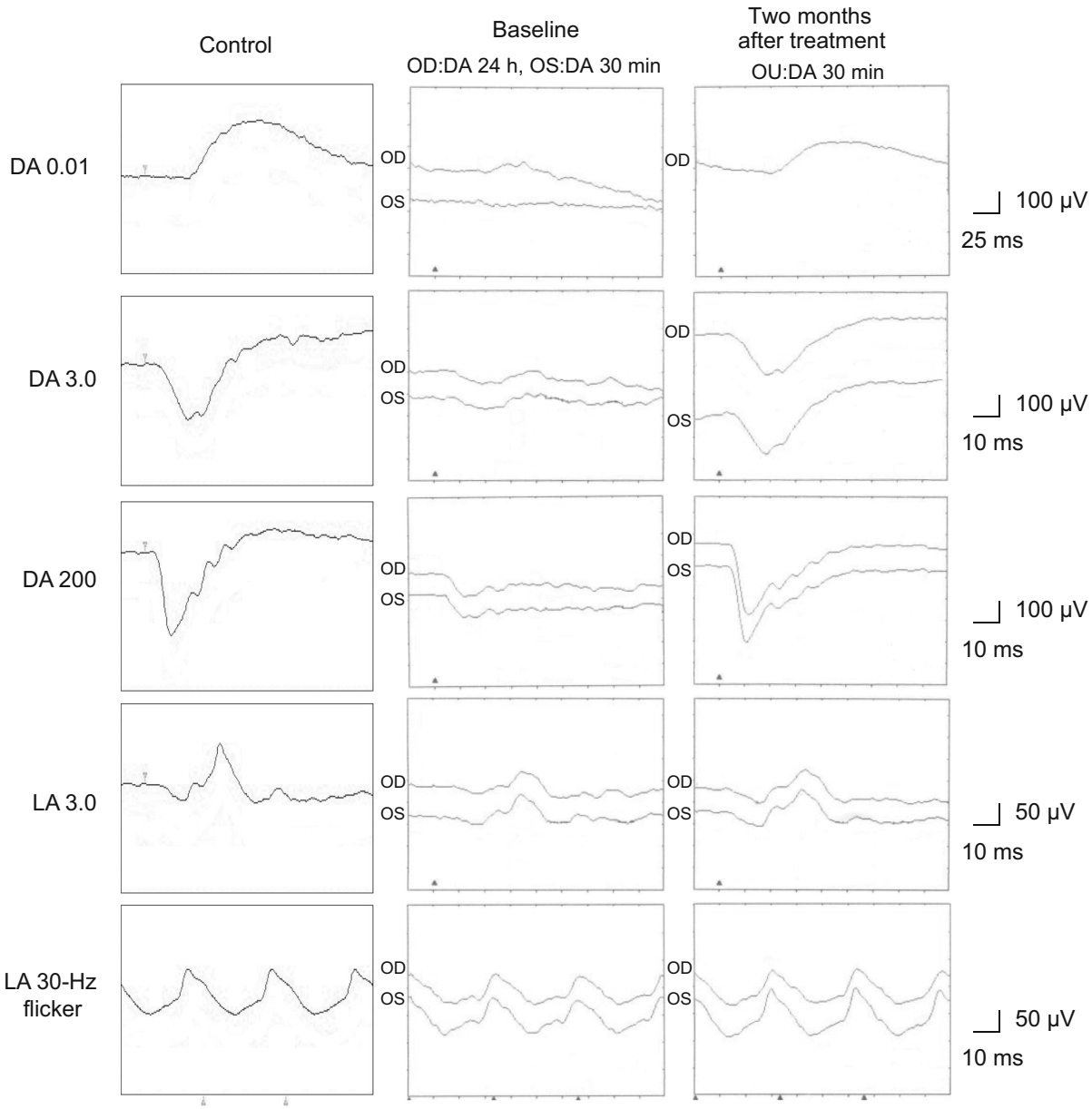

Fig. 2 Full-field electroretinograms**.** Full-field electroretinograms (ERG) of a control and this patient at baseline (24-h [h] dark adaptation [DA] in the right eye [OD] and 30-min [min] DA in the left eye [OS]) and at two months after treatment commencement (30-min DA in both eyes [OU]). For scotopic ERG, dark-adapted (DA) 0.01 cd s/m^2 (DA 0.01) ERG, DA 3.0 ERG and DA 200 ERG were recorded. For photopic ERG, light-adapted (LA) 3.0 ERG and LA 30-Hz flicker ERG were recorded

105 mg/dl (normal range: 70 − 139 mg/dl), both were within normal range. Consequently, retinol palmitate was administered at a dosage of 10,000 IU/day for the next two months, and subjective symptoms improved within 20 days after starting treatment. Two months after treatment commencement, the serum vitamin A level was within the normal range (283 IU/dL). ERG was performed again in OU after dark adaption for 30 min (Fig. 2). On DA 0.01 ERG, b-wave amplitudes in OD had improved to 50% of our controls [12]. On DA 3.0 and DA 200 ERG, a-wave amplitudes had improved to

70% and 85% of the controls, respectively, whereas b-wave amplitudes had improved to 65% of the controls. Responses to LA 3.0 and LA 30-Hz flicker ERGs were also slightly improved in comparison with baseline.

Discussion

In this report, we have described the case of a 58-year-old patient undergoing hemodialysis who presented with progressive photophobia and night blindness and was found to have numerous white dots in bilateral midperipheral retinae (Fig. 1) and extremely reduced responses in DA 0.01 ERG (Fig. 2).

Although this patient's differential diagnosis initially included fundus albipunctatus, retinitis punctata albescens, and paraneoplastic retinopathy, paraneoplastic retinopathy was ruled out due to a lack of a cancer history, and IRDs were also ruled out by the WES analysis. Subsequently, the patient was found to have a low serum vitamin A level and was diagnosed with VAD. He denied a history of bariatric surgery or hepatobiliary/pancreatic diseases, although these conditions are often responsible for VAD in industrialized nations [6]. Since patients with renal insufficiency undergoing hemodialysis often have high levels of serum vitamin A/retinol due to reduced glomerular filtration of RBP4 [7], it was unusual for this patient to present with VAD. There has been one report of two Japanese hemodialysis patients with VAD caused by the use of non-calcium-containing phosphate binders during maintenance hemodialysis, leading to low levels of both serum LDL cholesterol and vitamin A due to impaired lipid absorption [18]. However, our patient did not use the non-calcium-containing phosphate binders, and his serum LDL cholesterol concentration was within normal range.

At baseline ERG of our patient, the b-wave amplitude in OD of DA 0.01, dark-adapted for 24 h, showed 15% of our controls in amplitude, whereas that in OS, dark-adapted for 30 min, was extinguished (Fig. 2). The substantial amplitude in OD by delayed dark adaptation was also seen in patients with fundus albipunctatus and Oguchi disease (OMIM #258,100, #613,411) [16, 17, 19]. A significant common finding of VAD, fundus albipunctatus, and Oguchi disease is the presence of potentially functional rod photoreceptors. On the other hand, the photopic responses were greater than the rod responses at baseline (Fig. 2). Two months after treatment commencement, the amplitudes in OU, dark-adapted for 30 min, were markedly recovered in DA 0.01, DA 3.0, and DA 200 ERG (Fig. 2). The recovered scotopic responses were still decreased compared with those of our controls, indicating rod photoreceptor loss to some extent. Taken together, rod photoreceptors are more vulnerable to VAD than cone photoreceptors as previously reported [3, 20, 21]. In previous reports, decreased scotopic and photopic ERG amplitudes have been recovered to normal amplitudes after vitamin A treatment in some VAD patients [3, 20, 22], whereas there has been a patient who does not recover to normal [21]. Our ERG results indicate that VAD may cause irreversible change, eventually rod photoreceptor death to some extent.

There have been some reports that have documented the presence of retinal dots/flecks related to VAD [20, 21, 23–25], although the mechanism of development of the white dots/flecks remains to be unresolved. Similarly, numerous white dots/flecks are seen in midperipheral to peripheral retinae of patients with fundus albipunctatus caused by biallelic *RDH5* variants [10, 15, 16]. Previous studies using cultured cells and *Rdh5* knockout ($Rdh5^{-/-}$) mice have revealed that white dots/spots may be related to the accumulation of cis-retinyl esters in the retinal pigment epithelium (RPE) [26, 27]. In fact, a recent electron microscopic study has demonstrated that low-density vacuoles were accumulated in the RPE of the $Rdh5^{-/-}$ mice, leading to development of the white dots/spots [28]. A similar pathomechanism might be responsible for development of white dots/flecks in VAD patients as seen in our patient. On the other hand, VAD patients without fundus white dots/flecks have been also reported [3, 29–31]. In one of those patients, night blindness had lasted for 3 years before diagnosis of VAD [30]. Therefore, it should be noted that the mechanism of how the white dots/flecks develop in VAD patients remains to be elucidated.

According to the "Japanese Meal Absorption, Standard (2020 edition)" report, provided only in Japanese, (https://www.mhlw.go.jp/stf/newpage_08517.html) published by the Ministry of Health, Labour and Welfare of Japan, a 58-year-old Japanese male has an estimated average daily requirement of 600–650 μg (retinol activity equivalents: RAE) of vitamin A; however, a 100-g cup of noodles or a 100-g

serving of retort curry contains only 3 μg and 8 μg of Vitamin A, respectively, according to the Food Composition Database of the Ministry of Education, Culture, Sports, Science and Technology of Japan. Therefore, his vitamin A intake had likely been far below this daily requirement for some time.

In summary, we have described ophthalmological findings in a Japanese patient undergoing hemodialysis who presented with night blindness and was found to have VAD. Although hemodialysis patients tend to have high levels of serum vitamin A, VAD can still occur in these patients if they are malnourished secondary to prolonged intake of an unbalanced diet. Therefore, VAD should always be considered in the differential diagnosis of night blindness, even in hemodialysis patients residing in industrialized nations.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Statements of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Patient consent The patient has consented to the submission of the case report to the journal.

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