

Vitamin A deficiency retinopathy related to medical interventions in a Swiss cohort: a case series

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Summary

AIMS OF THE STUDY: Vitamin A deficiency retinopathy is a potentially blinding disease. In developed countries, vitamin A deficiency due to malnutrition is rare. However, vitamin A deficiency can be caused by malabsorption resulting from bowel resection or medication. In this retrospective study, we present five cases of vitamin A deficiency retinopathy related to malabsorption secondary to medical interventions.

METHODS: Electronic charts over a ten-year period (2012–2022) were screened for vitamin A deficiency retinopathy. Only patients with vitamin A deficiency confirmed by laboratory tests were included. Symptoms, medical history, visual acuity, optical coherence tomography, fundus autofluorescence, electrophysiological examination, and vitamin A levels were reviewed.

RESULTS: Five eligible cases were identified. Median age was 44.7 years (range 22.2–88.9), median duration of ocular symptoms prior to diagnosis was 14 months, and median visual acuity was 1.0 (range 0.5–1.0, Snellen, decimal). Three patients had a history of bariatric surgery, one patient had a small bowel resection and was on octreotide treatment, and one patient suffered from cystic fibrosis and had a history of small bowel resection and severe hepatopathy. Optical coherence tomography showed various abnormalities, including a reduced interdigitation zone, subretinal drusenoid deposits, and a thinned outer nuclear layer. Electroretinogram findings ranged from abnormal oscillatory potentials to non-recordable rod responses.

CONCLUSIONS: Vitamin A deficiency retinopathy can occur following medical interventions associated with malabsorption. In cases of night blindness, vitamin A levels should be measured.

Introduction

Humans obtain vitamin A as the preformed vitamin retinol or as its provitamins, the carotenoids. All are fat soluble. In the small intestine, dietary retinyl esters are hydrolysed by pancreatic enzymes to unesterified retinol [1]. Retinol, in addition to dietary carotenoids, is then absorbed into the

enterocytes. Retinol is subsequently either re-esterified and joins with carotenoids to form chylomicrons, which enter the lymphatic system, or enters directly into the portal blood system via a lipid transporter. The liver stores vitamin A and normally contains a reserve sufficient for six months to two years [1–3]. Vitamin A is crucial for the physiological function of photoreceptors [4–6].

In developed countries, vitamin A deficiency due to malnutrition is rare. The World Health Organization global database on vitamin A deficiency excludes countries with a per capita gross domestic product of >15,000 USD because their levels of vitamin A deficiency are assumed to be too low to be of significance for public health. However, vitamin A deficiency can arise due to malabsorption secondary to bowel shortening, for example in cases of bariatric surgery; as a side effect of medication [7–12]; or as a result of disease, such as cystic fibrosis [9]. Micronutrient deficiency is a well-known problem after bariatric surgery and can occur even with preventive supplemental intake [10, 13]. Deficiencies tend to increase over time as storage is depleted. In contrast to vitamin D or calcium levels, vitamin A levels are not routinely monitored after bariatric surgery, permitting the development of clinical manifestations of vitamin A deficiency, such as night blindness or xerophthalmia. A similar issue occurs with medication that increases fatty stools, such as somatostatin analogues, which can lead to deficiency in all fat-soluble vitamins, including vitamin A [8].

The typical manifestation of vitamin A deficiency retinopathy is night blindness, which is mainly caused by an elevated rod threshold due to reduced rhodopsin levels. This results in reduced dark adaptation [14]. In milder cases, dark adaptation is achieved but as a slower rate [14, 15]. Cones are affected only in very severe and long-lasting vitamin A deficiency [14, 15]. Changes in electrophysiological examinations were described by Arden in 1964 [16]. He noted a diminished electroretinogram response and an abnormal electrooculogram in a patient with vitamin A deficiency who was experiencing night blindness. More recent reports describe the typical electroretinogram findings as reduced or absent rod responses in the presence of preserved light-adapted single flash and reduced 30 Hz flicker responses [17, 18]. Results of retinal imaging are variable,

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likely depending on the severity and duration of the vitamin A deficiency. Fundus autofluorescence typically indicates various degrees of speckled patches of hypoautofluorescence [19]. Optical coherence tomography can detect abnormal outer retinal foveal hyperreflectivity, disappearance of the interdigitation zone, disruption of the ellipsoid zone, white spots resembling subretinal drusenoid deposits typical of age-related macular degeneration, and thinning of the outer nuclear layer [19–25]. These findings are not specific to vitamin A deficiency retinopathy and exhibit high interindividual variability. Due to the rarity of vitamin A deficiency retinopathy, the fundus autofluorescence and optical coherence tomography findings may be easily missed or attributed to a different retinal pathology.

In this case series, we consider five patients who developed likely iatrogenic symptomatic vitamin A deficiency retinopathy, either following surgical intervention or as a side effect of medication.

Materials and methods

For this single-centre retrospective case study the electronic health records of the Department of Ophthalmology at the University Hospital of Zurich were used as a database. All authors have access to these electronic health records by virtue of their employment at the Department of Ophthalmology. The clinic information system used at the department (KISIM, CISTEC AG, Zurich, Switzerland) has an integrated algorithm for keyword searches, operable only by designated staff after approval from the hospital's data governance board. For this study, only records of patients who had previously provided informed general consent for further use of their data for research purposes were searched. The records between January 2012 and April 2022 were electronically screened for keywords including vitamin A deficiency as well as bariatric surgery or variations thereof (see figure 1 for detailed list). The search was performed on the free texts of the record entries in the designated field for diagnosis using OR (not exclusive) logic. This search strategy results in positive hits in case of negation, such as “no vitamin A deficiency”, but misses cases with misspelled diagnoses. Only the first positive hit per patient was returned to avoid duplication. The resulting records of this search were then manually screened by a physician for a true diagnosis of vitamin A deficiency retinopathy, especially by abnormalities in the outer retinal layers as detected by retinal imaging and abnormal electrophysiologic examination. Only cases with laboratory-confirmed vitamin A levels below normal (lower limit of the normal range is 0.30 mg/l at our laboratory) and history of a medical intervention likely causing or related to vitamin A malabsorption were included. Symptoms, duration of symptoms, visual acuity, and vitamin A levels were recorded. Results of optical coherence tomography, fundus autofluorescence, electroretinograms, and dark adaptation tests were reviewed if available. Electroretinograms were performed according to the International Society for Electrophysiology of Vision (ISCEV) guidelines valid at the respective time [26, 27]. Further relevant medical history, especially history of bariatric surgery, liver disease, or specific medication known for hindering fat-soluble vitamin uptake, was noted, including the time between any intervention and diagnosis of vitamin A deficiency retinopathy.

For the database search, KISIM (CISTEC AG, Zurich, Switzerland) has been used.

Statistics were performed using IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp). Median and range were calculated for age, duration of symptoms prior to diagnosis, visual acuity, and vitamin A levels (as data could not be assumed to be normally distributed).

The study was conducted in accordance with the Declaration of Helsinki and approved by the Cantonal Ethics Committee of Zurich (Basec no. PB_2016-00264, initially approved January 2016, extension approved October 2018).

Results

The initial electronic database search found 116 possible patients. After manual verification of these electronic health records, five patients had laboratory-confirmed vitamin A deficiency retinopathy and history of a medical intervention or medication likely causing or related to a vitamin A malabsorption (figure 1, tables 1 and 2). Median age was 44.7 years (range 22.2–88.9 years). All patients were female. The presenting symptom in all patients was night blindness, in one case combined with tunnel vision. Median duration of symptoms prior to diagnosis was 14 months (range 1–16 months). Median visual acuity was 1.0 (range 0.5–1.0, Snellen, decimal). Median vitamin A level was 0.07 mg/l (range 0.06–0.24 mg/l); the local normal range is 0.30–0.70 mg/l.

Summary of all cases

All patients had visible alterations of the outer retinal layers shown by optical coherence tomography (figure 2). These ranged from minimal irregularity to a complete absence of the interdigitation zone or an altered ellipsoid zone. Patients also varied in the presence of subretinal drusenoid deposits. Fundus autofluorescence showed varying degrees of speckled patches of hypofluorescence in four patients (the remaining patient did not undergo fundus autofluorescence imaging) (figure 3). Electroretinogram findings varied widely from abnormal oscillatory potentials to reduced or delayed mixed rod–cone a- and/or b-waves to non-recordable rod responses (for details see table 2). Three patients had dark adaptation tested, and all findings were pathological (figure 4). Two patients displayed abnormally slowed dark adaptation with reduced sensitivity throughout the 30-minute testing period, while the other patient exhibited no reproducible change in sensitivity over the test duration. In terms of associated systemic history, three patients underwent bariatric surgery (all gastric bypasses) three, seven, and nine years prior to diagnosis of vitamin A deficiency retinopathy, respectively. One patient had a small bowel resection 10 years prior and had been on octreotide treatment for eight years due to

Table 1:
Demographic data.

Patients included (n)		5
Gender	female/male	5/0
Age (years)	median (range)	44.7 (22.1–88.9)
Visual acuity (Snellen, decimal)	median (range) in right/left eye	1.0 (0.8–1.0) / 1.0 (0.5–1.0)
Duration of symptoms until diagnosis (months)	median (range)	14 (1–16)

Figure 1: Study selection process flow chart.

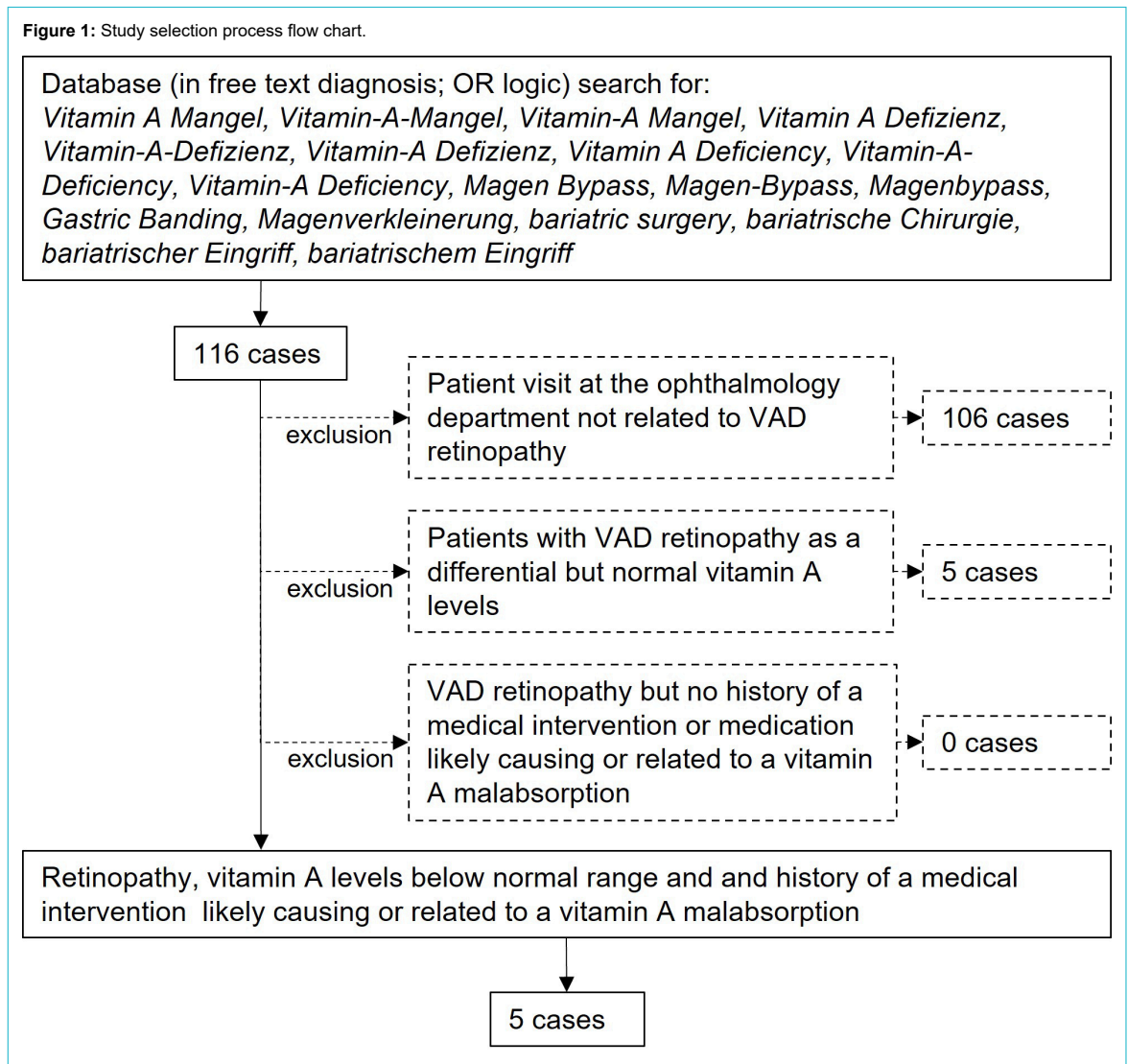


Table 2:

Overview of all cases.

ID/g	Age (years)	Symptoms	Duration (years)	VA right	VA left	Vit A level (mg/l)	ERG abnormalities	DA	OCT	FAF	Systemic associated disease
1/f	88.9	Night blindness	1.4	1.0	0.5	0.08	Non-recordable rod responses. Reduced and delayed mixed rod-cone a- and b-waves with pseudo-negative configuration.	n/a	Thinned ONL, atrophic EZ, subretinal drusenoid deposits.	speckled	NET, small bowel resection 10 years prior, octreotide treatment for 8 years.
2/f	51.7	Night blindness	1.4	1.0	1.0	0.06	Reduced mixed rod-cone a-wave amplitudes	Slowed and reduced	Slightly reduced interdigitation zone	speckled	Gastric bypass surgery 9 years prior
3/f	44.7	Night blindness	0.8	1.0	1.0	0.07	Abnormal OP	Slowed and reduced	Reduced interdigitation zone, foveal hyper-reflective outer retinal lasers	n/a	Gastric bypass surgery 7 years prior
4/f	40.7	Night blindness tunnel vision	1.2	0.8	0.8	0.24	Delayed mixed rod-cone a- and b-waves, asymmetric abnormal OP	n/a	Subretinal drusenoid deposits	speckled	Gastric bypass surgery 3 years prior
5/f	22.2	Night blindness	0.1	1.0	1.0	0.06	Non-recordable rod responses. Reduced mixed rod-cone a- and b-wave amplitudes with supernormal b-wave peak time (comparable to single flash cone b-wave peak time), abnormal OP	Severely reduced	Missing interdigitation zone	speckled	Cystic fibrosis; ileum and jejunum resection 12 and 4 years prior, severe hepatopathy; history of lung transplantation

DA: dark adaptation, ERG: electroretinogram, EZ: ellipsoid zone, f: female, FAF: fundus autofluorescence, g: gender, ID: identification number, n/a: not applicable, NET: neuroendocrine tumor, OCT: optical coherence tomography, ONL: outer nuclear layer, OP: oscillatory potentials, VA: visual acuity.

a neuroendocrine tumour. Another patient had a history of cystic fibrosis; ileum and jejunum resections 12 and four years prior, respectively; lung transplantation; and severe hepatopathy of mixed origin, possibly secondary to poly-medication.

Detailed findings of one representative case

An 87-year-old female (patient 1, table 2) presented at the emergency clinic of the Department of Ophthalmology after suffering bilateral visual disturbances for one to two months. She had a history of breast cancer, which was diagnosed the same year and treated surgically, followed

Figure 2: Subfoveal optical coherence tomography. (a) Exemplary healthy retina. (b) Vitamin A deficiency retinopathy, presenting abnormal outer retinal foveal hyperreflectivity (white arrow) and a reduced interdigitation zone (black double arrow). (c) Vitamin A deficiency retinopathy, revealing subretinal drusenoid deposits (arrow heads). EZ: ellipsoid zone; ONL: outer nuclear layer; RPE: retinal pigment epithelium.

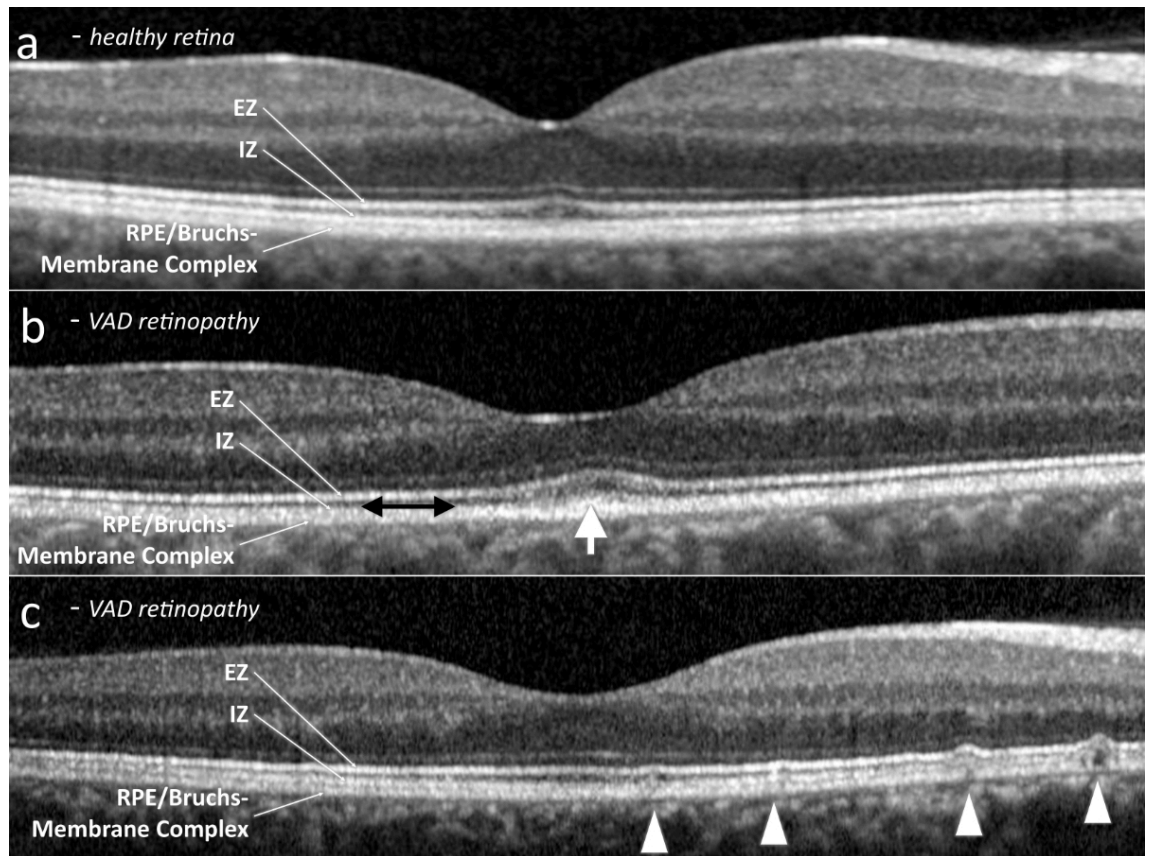
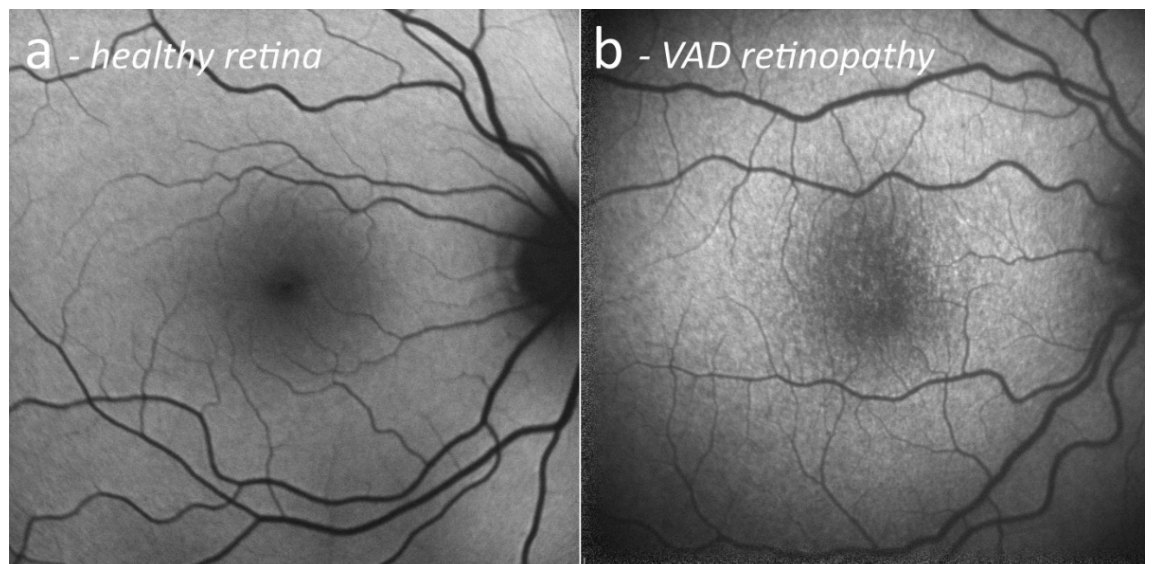


Figure 3: Fundus autofluorescence. (a) Exemplary healthy retina. (b) Vitamin A deficiency retinopathy, presenting speckled hypoautofluorescent patches at the posterior pole.

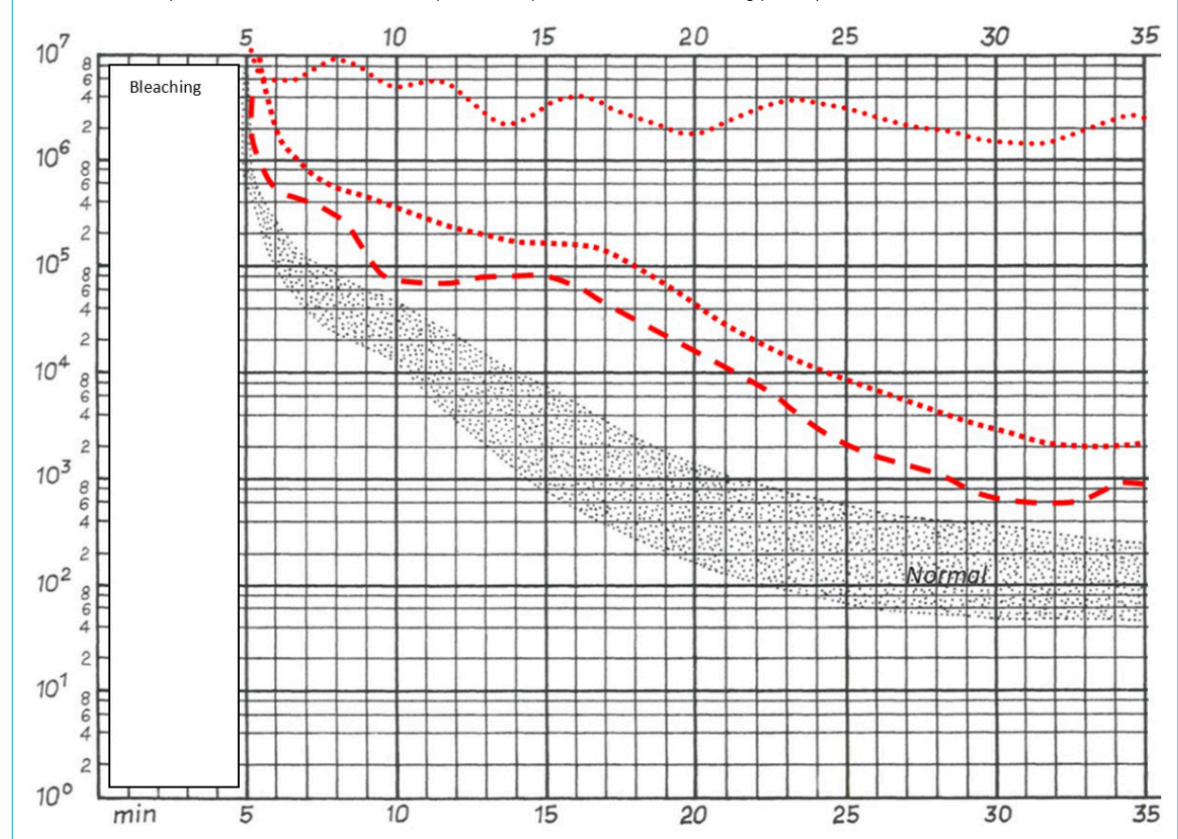


by ongoing treatment with tamoxifen. She had a further history of a neuroendocrine tumour of the small bowel, which had been diagnosed ten years prior and had been treated surgically with a small bowel resection and adjuvant chemotherapy, and she was receiving ongoing treatment with octreotide (Sandostatin®). Ocular findings in both eyes included non-exudative age-related macular degeneration and pseudoexfoliation glaucoma. A trabeculectomy had previously been performed in the left eye. Since this operation, the pupil had not been reactive to mydriatic eye drops. Visual acuity was 0.6 in the right and 0.4 in the left eye. Slit-lamp examination showed a cataract in the right eye and pseudophakia with posterior capsule opacification in the left eye. Fundus biomicroscopy revealed numerous round, yellow-white lesions along the temporal arcades at the posterior pole and nasally to the optic nerve in both eyes. These lesions resembled subretinal drusenoid deposits on optical coherence tomography (figure 5).

We arranged further investigations into the patient's symptoms in our general ophthalmology clinic; however, she decided to return to her ophthalmologist in private practice and cancelled the hospital appointments. Twelve months later, she was referred to our clinic for exacerbation of her visual disturbances, notably increasing night blindness, which she initially described as "everything gets darker and darker". Visual acuity was 0.6 in the right and 0.5 in the left eye. Again, optical coherence tomography showed numerous subretinal drusenoid deposits resembling lesions (figure 5). Additionally, there was a noticeable thinning of the outer nuclear layer compared to one year prior, as well as marked alterations of the ellipsoid zone and

the interdigitation zone. Fundus autofluorescence presented bilateral speckled patches of hypoautofluorescence and some hyperautofluorescence (figure 5). Electrophysiological examination showed non-recordable rod responses, pseudo-negative mixed rod-cone electroretinogram configurations [28], and reduced 30 Hz flicker responses (figure 6). Dark adaptation testing was not performed. Blood tests revealed a vitamin A level of 0.08 mg/l (lower limit of local normal range 0.30 mg/l). The patient was also tested for the presence of anti-recoverin, anti-enolase, and anti-retina IgGAM antibodies, none of which were detectable. Oral supplementation of vitamin A (30,000 IE daily) was initiated immediately. The patient did not notice any improvement within the first two weeks. However, after two months she reported a marked improvement of her symptoms. At that time, vitamin A levels were within normal limits (0.43 mg/l). Optical coherence tomography showed milder alterations of the ellipsoid zone and the interdigitation zone and fewer subretinal drusenoid deposits, as well as a slight increase in the thickness of the outer nuclear layer. Fundus autofluorescence revealed fewer speckled patches. An electroretinogram indicated noticeably improved scotopic responses, including clearly measurable rod responses. A pseudo-negative configuration was no longer present. Due to the postoperative anisocoria described above, with a non-dilating left pupil, the results of both electroretinogram examinations were asymmetric (right eye > left eye).

Figure 4: Dark adaptation of patients 2, 3 and 5. Patients 2 (square box line) and 3 (dashed line) displayed abnormally slow dark adaptation with reduced sensitivity throughout the 30-minute testing period. Patient 5 (dotted line) exhibited no reproducible increase in sensitivity over the test duration. (Note: the first five minutes correspond to the pre-measurement bleaching period.)



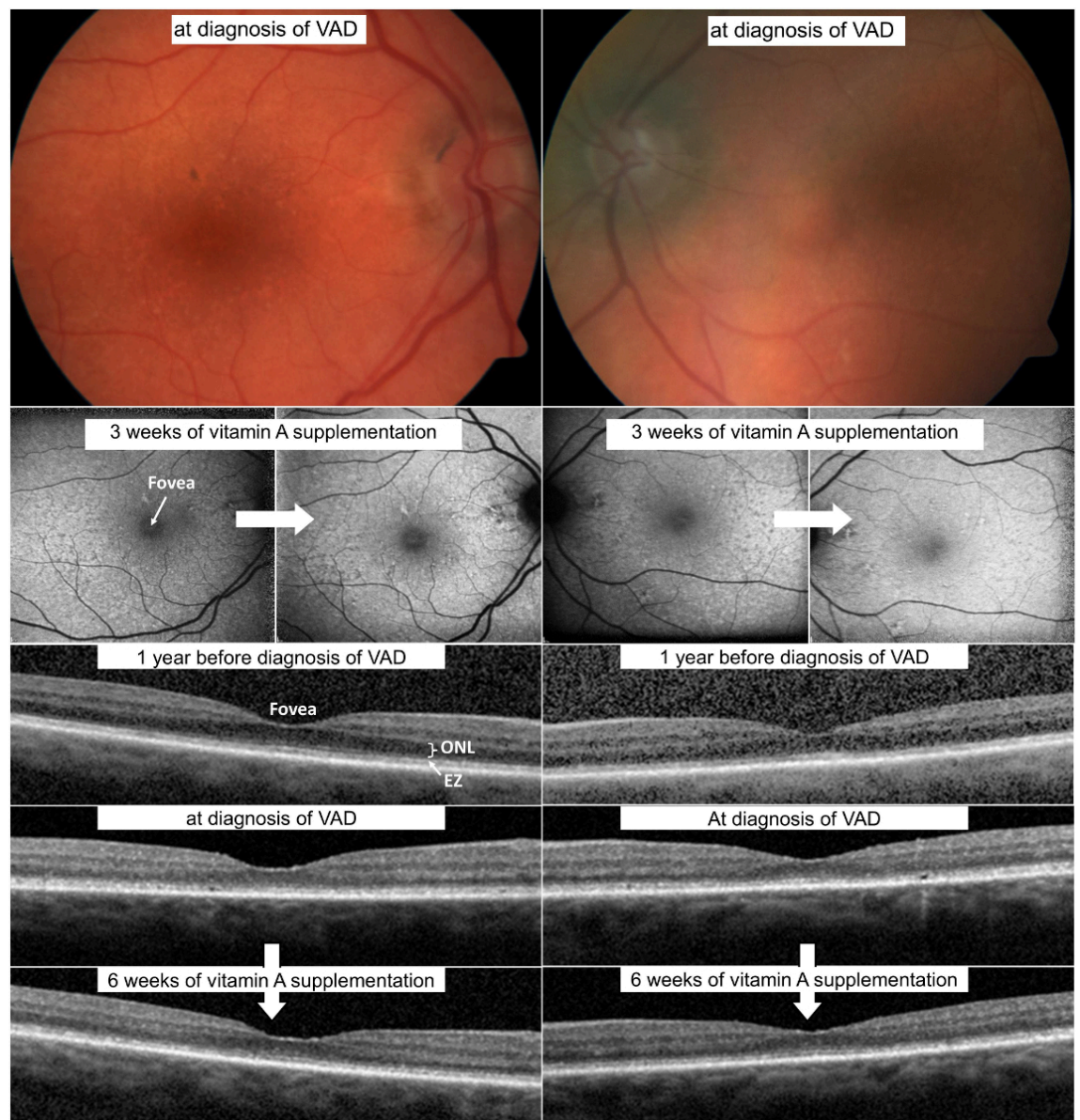
Discussion

In countries where malnutrition is uncommon, vitamin A deficiency is a rare occurrence; therefore, the time between first symptoms and diagnosis can be prolonged. Vitamin A deficiency retinopathy is generally a reversible disease but can progress to permanent blindness if left untreated [4, 20, 29–33]. All our patients presented with night blindness, reinforcing the importance of considering a thorough history of a patient's visual symptoms, as patients will note various visual issues but may not perceive them as night blindness. In cases of vitamin A deficiency, rods are known to be affected before cones, likely due to the provision of 11-cis-retinal through the Müller cells [6, 34]. Furthermore, it seems that not all types of cones are affected simultaneously, with S-cones being affected first [34]. Publications

documenting electroretinograms in patients with vitamin A deficiency have described an earlier and more extensive rod involvement, and cone electroretinograms can indicate a reduced amplitude or longer latency [35–37]. Full-field electroretinograms showed diverse abnormalities of variable severity in all five patients in accordance with the previous publications discussed above. In our cohort, the three patients who were tested for dark adaptation all showed pathological findings, fitting their symptoms.

Optical coherence tomography and fundus autofluorescence findings agree with previously published results [19–23, 32]. Our cases show changes of differing severity at the level of the ellipsoid zone and interdigitation zone, in some cases combined with alterations of the retinal pigment epithelium and subretinal drusenoid deposits. In one

Figure 5: Multimodal imaging of patient 1. (a) Fundus photography at time of diagnosis of vitamin A deficiency. Note the numerous round, yellow-white lesions at the posterior pole in both eyes. (b) Fundus autofluorescence at baseline with speckled patches of hypoautofluorescence and some hyperautofluorescence and after vitamin A supplementation, showing a reduction of the speckled patches. (c) Optical coherence tomography one year before diagnosis of vitamin A deficiency, at diagnosis of vitamin A deficiency, and after vitamin A supplementation. Note the thinning of the outer nuclear layer before vitamin A deficiency diagnosis and partial recovery after supplementation. Additionally, an altered ellipsoid zone and interdigitation zone are visible, in addition to subretinal drusenoid deposits, also demonstrating partial recovery after supplementation. EZ: Ellipsoid zone; ONL: Outer nuclear layer.

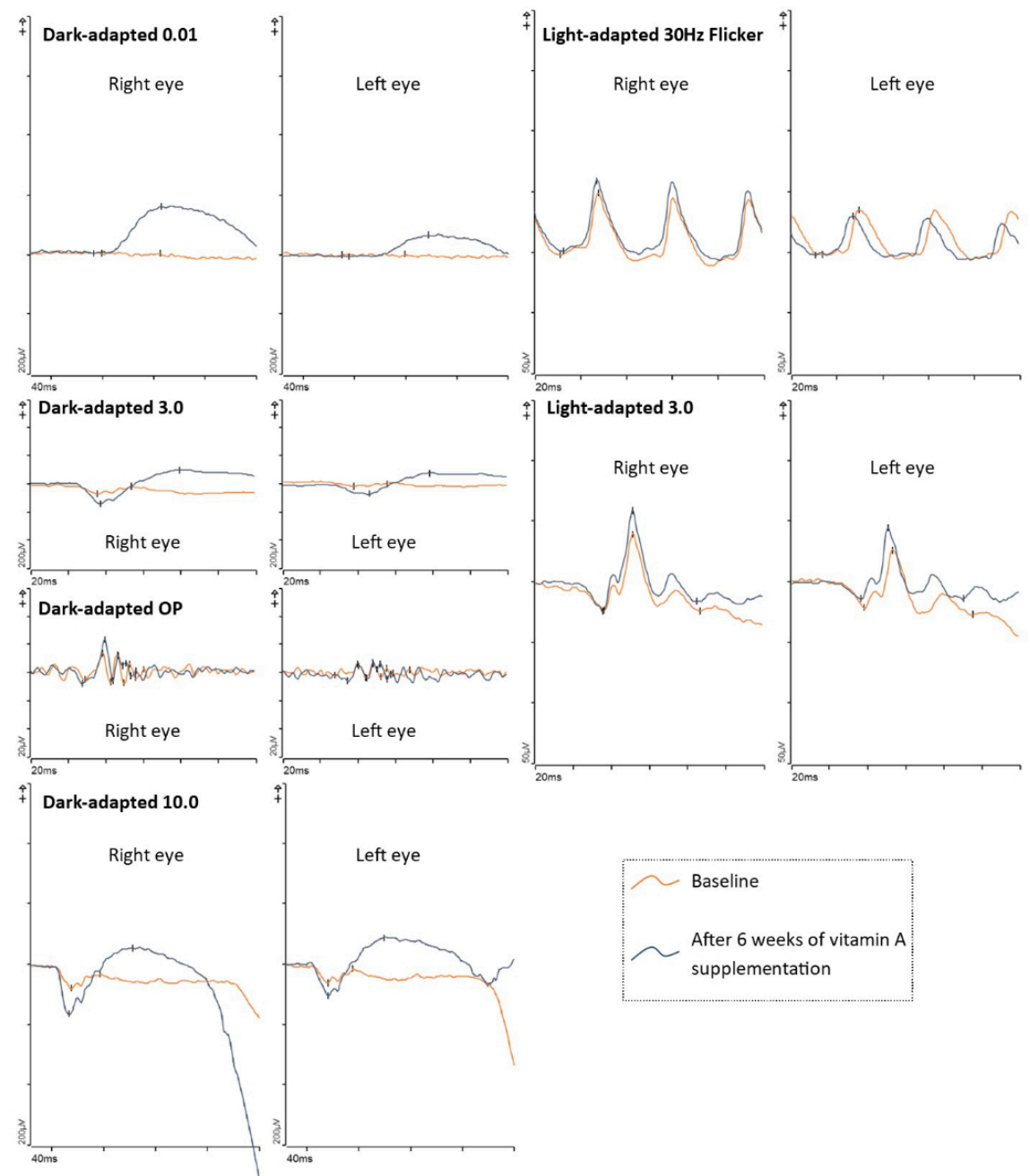


case, we observed a thinning of the outer nuclear layer. Subtle changes may easily be missed or dismissed as image noise; others can be hard to separate from changes due to age-related macular degeneration, which is (depending on age) a far more common disease. This again emphasizes the importance of careful examination of medical history, as age-related macular degeneration would more likely be associated with decreased reading ability or central scotoma and less likely with night blindness. In uncertain cases, a full-field electroretinogram may help to distinguish between age-related macular degeneration and vitamin A deficiency retinopathy. Subretinal drusenoid deposits in age-related macular degeneration can have the

same appearance as in vitamin A deficiency retinopathy but would not lead to an altered full-field electroretinogram with non-recordable rod responses [38].

In all our cases, the surgical interventions or medical treatments had taken place several years prior to the first symptoms of vitamin A deficiency retinopathy, which is in accordance with reports of other micronutrient deficiencies [7, 12, 13, 39]. Due to this time lag, a patient often might not connect their vision problems to their earlier medical history and might not spontaneously inform their ophthalmologist about these interventions or medication intake. In cases of night blindness, doctors, especially ophthalmologists, should ask specifically about a history of bariatric or

Figure 6: Electrophysiological examination of patient 1 at baseline and after vitamin A supplementation. Baseline shows non-recordable rod responses, pseudo-negative mixed rod-cone electroretinogram configurations, and reduced 30 Hz flicker responses. After six weeks of vitamin A supplementation, the electroretinogram showed noticeably improved scotopic responses, including clearly detectable rod responses (dark-adapted 0.01). A pseudo-negative configuration was no longer present. Note: The results of both electroretinogram examinations were asymmetric (right eye > left eye) due to a non-dilating left pupil. ERG: Electroretinogram; OP: Oscillatory potentials.



other gastrointestinal surgery and for a complete list of the patient's current medications. In cases of night blindness with possible vitamin A deficiency due to a patient's medical history or suggestive imaging findings, vitamin A levels should be measured.

The main limitation of our study is the small and mixed cohort. Further, our database search was limited to patients who had already signed a general consent form permitting the use of their health-related data for research purposes prior to the search. The number of patients with vitamin A deficiency retinopathy treated at the department who did not sign the general consent form is unknown. Generalisation of the findings is therefore limited. Further, vitamin A levels are not routinely measured in ophthalmologic workups in developed countries, and retinopathies might be misdiagnosed. Therefore, there is a possibility of under-reporting vitamin A deficiency retinopathy.

Data sharing

Further imaging data can be found in the supplementary material. More detailed information cannot be released to protect patient confidentiality.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

More optical coherence tomography and fundus autofluorescence images are available below.

Figure S1: Subfoveal optical coherence tomography scans of patients 2–5. (a) Patient 2 with slightly reduced interdigitation zone. (b) Patient 3 with abnormal foveal outer retinal hyperreflectivity and reduced interdigitation zone. (c) Patient 4 revealing drusenoid deposits. (d) Patient 5 with reduced interdigitation zone.

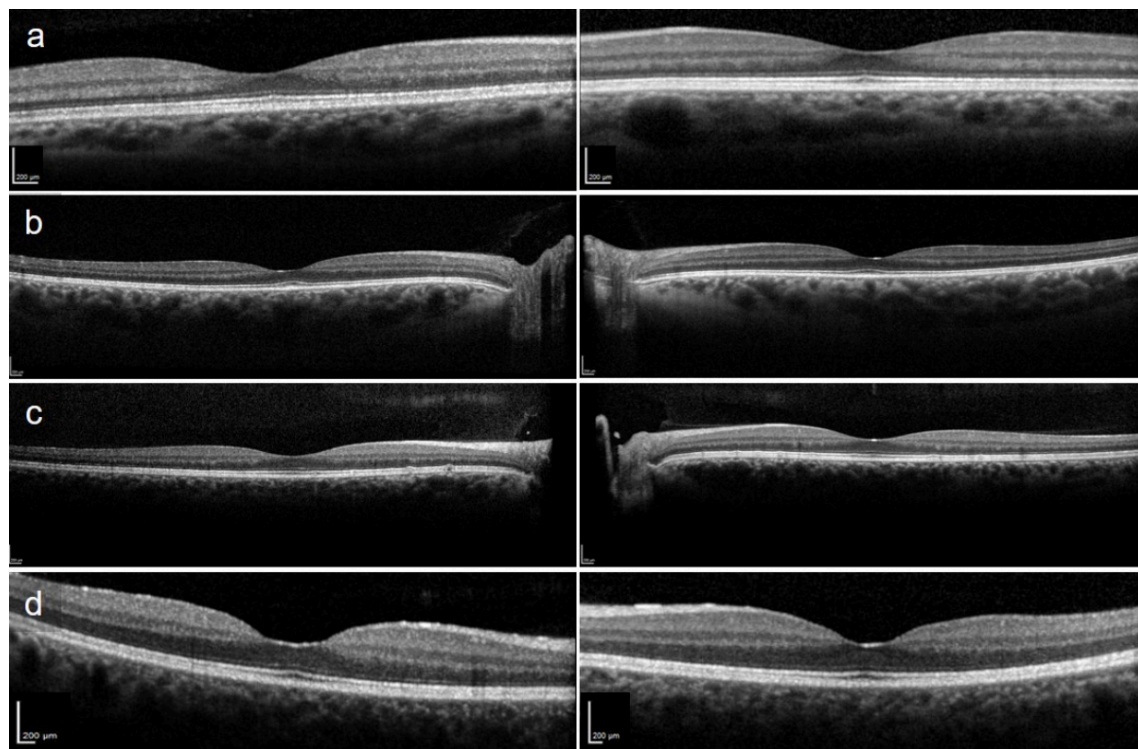


Figure S2: Fundus autofluorescence of patients (a) 2, (b) 3 and (c) 5. All presenting speckled hypoautofluorescent patches at the posterior pole.

