Case Report: Nyctalopia Due to Severe Liver Cirrhosis–induced Vitamin A Deficiency

Shuyi Chen, OD[1]* and Amy Jill Quan, OD, FAAO[1]

SIGNIFICANCE: Vitamin A is a micronutrient critical for retinal function. Patients with a deficiency may notice a progressive decline in night vision as rod photoreceptors become unable to regenerate rhodopsin. Although uncommon in developed nations, vitamin A deficiency should be considered in symptomatic patients with chronic, severe liver disease.

PURPOSE: This report presents a rare case of night blindness secondary to poor vitamin A metabolism due to severe liver cirrhosis.

CASE REPORT: A 62-year-old White woman presented with progressively worsening vision in dim lighting over the past 6 to 8 months. She was asymptomatic in daylight but "blind in the dark" to the extent that she was afraid to go outside at night. She had no personal or family history of night blindness or retinal disorders. Ocular health was unremarkable with dilation. Given her medical history of severe nonalcoholic liver cirrhosis, malabsorption of vitamin A was suspected and subsequently confirmed by the very low vitamin A level in her serum analysis. The patient was sent to endocrinology for evaluation, and appropriate repletion therapy was implemented. Subjective improvement in symptoms, along with better performance on visual field testing, was noted after initiating oral vitamin A supplementation for 5 months.

CONCLUSIONS: Although vitamin A deficiency is a relatively rare disorder in the United States, it should be suspected in patients with severe liver disease or other conditions causing malabsorption who experience a loss of night vision.

Author Affiliations:
[1]Perry Point VA Medical Center, PerryPoint, Maryland
*drsuzychen@gmail.com

Optom Vis Sci 2023;100:174–177. doi:10.1097/OPX.0000000000001982

Vitamin A is a fat-soluble vitamin ingested in the diet and absorbed through the small intestine as either retinol or carotene.[1] It is esterified to retinyl palmitate in the liver, where up to 80% of vitamin A in the body is stored.[1] Retinyl palmitate can be hydrolyzed back to retinol, which then gets transported to target tissues. Vitamin A has several important roles in ocular metabolism: on the ocular surface, it is necessary for the synthesis of RNA and glycoprotein in corneal and conjunctival epithelial cells; in the retina, retinol serves as the backbone of photosensitive pigment in rods and cones.[2] The aldehyde form of vitamin A, retinal, is the crucial chromophore that combines with rod and cone opsins to form rhodopsin and activated cone opsins, which are essential for phototransduction.

As a result, vitamin A deficiency has a wide range of ophthalmic manifestations, including corneal and conjunctival xerosis, keratomalacia, retinopathy, and night blindness.[2,3] Because rod photoreceptors are more sensitive to vitamin A deficiency than cone photoreceptors, nyctalopia is often the earliest and most common symptom of vitamin A deficiency.[4] If left untreated, cone receptors may also become affected and cause a decrease in visual acuity and color vision, ultimately leading to permanent vision loss.[5]

Vitamin A deficiency is prevalent in developing nations with underserved populations, mainly because of malnourishment of children and pregnant women.[6] According to the World Health Organization, vitamin A deficiency is the leading cause of childhood blindness in the developing world.[7] Although vitamin A deficiency is uncommon in developed nations, it can occur as a result of malnutrition, malabsorption, or impaired vitamin metabolism secondary to liver disease.[4] In the literature, cases of vitamin A deficiency have been reported in patients with a history of gastric bypass and intestinal surgery.[8–10] This report presents a case of vitamin A deficiency with nyctalopia in a patient with severe liver cirrhosis that improved after supplementation with exogenous vitamin A. No identifiable health information was included in this report.

CASE REPORT

A 62-year-old White woman presented to the clinic with complaints of difficulty seeing and navigating at night that started 6 to 8 months ago. The patient had an ocular history of lid myokymia, dry eye syndrome, and posterior vitreous detachment in both eyes. Her medical history was positive for nonalcoholic liver cirrhosis, chronic kidney disease, osteoarthritis of the knee, irritable bowel syndrome, iron deficiency anemia, obstructive sleep apnea, bipolar disorder, impaired fasting glucose, hypertension, and hyperlipidemia. Systemic medications taken at the time of presentation included clonazepam, losartan, lurasidone, meloxicam, and rivaroxaban. These medications were not believed to be contributory to her chief complaint of night blindness. She had been prescribed cholestyramine, a bile acid sequestrant that could deplete fat-soluble vitamins, but she was unable to tolerate the medication because of

bad taste and only took it once. The patient had no history of surgery and showed no signs of malabsorption, as she denied having nausea, vomiting, diarrhea, or eating disorder. Family ocular and medical history were unremarkable. She had no other visual or ocular complaints and claimed to have good vision in illuminated settings (Fig. 1).

Best-corrected visual acuity was $20/20^{-2}$ in the right eye and 20/20 in the left eye with Snellen testing. Extraocular muscles, confrontation visual fields, and pupils were all normal. Upon slit-lamp examination, mild cortical and nuclear sclerotic cataracts were noted in both eyes. Her intraocular pressure was measured to be 19 mmHg in both eyes at 1:40 PM with Goldmann applanation tonometry. Dilated fundus examination revealed flat and intact macula, and normal optic discs with a cup-to-disc ratio of 0.3 in the right eye and 0.35 in the left eye. Rim tissues were pink and healthy in both eyes, with intact retinal nerve fiber layer as confirmed by optical coherence tomography (OCT). Retinal vasculature was normal without any signs of retinopathy. No peripheral retinal lesions were observed on binocular indirect ophthalmoscopy that would explain her entering complaint of nyctalopia.

Humphrey Visual Field 30-2 Swedish Interactive Testing Algorithm Fast was performed. In the right eye, dense peripheral field defects were noted superior nasally, extending to the superior-temporal and inferior-nasal quadrants (Fig. 2A). The left eye, naturally dark adapting for 10 minutes while the right eye performed the test, showed dense superior-temporal field loss approaching central fixation, extending into inferior-temporal and superior-nasal quadrants (Fig. 2B). After the left eye finished the test, the right eye had dark adapted for 23 minutes. Subsequent repeat visual field testing of the right eye showed deeper defects than on the initial test, some of which were absolute (Fig. 2C). False-negative errors were high on all the tests, likely because of the patient's dark adaptation issues.

Vitamin A deficiency–associated nyctalopia was suspected in this case given the patient's medical history of stage 4 nonalcoholic liver cirrhosis, which could result in malabsorption and low storage of vitamin A. Bloodwork was ordered and revealed a vitamin A level of 29 μg/dL, with normal reference range of 38 to 98 μg/dL. The deficiency was confirmed and relayed to the patient and her primary care doctor. The patient was evaluated by an endocrinologist, who subsequently started her on oral β-carotene supplementation at a dose of 25,000 IU per day.

The patient reported a subjective improvement of symptoms within weeks of initiating treatment. She noticed that she was able to identify the borders and shapes of objects in the dark that had previously appeared black and unrecognizable. The patient was followed closely by her endocrinologist, and repeat laboratory work after 2 months of supplementation indicated a vitamin A level of 32 μg/dL, improved but still subnormal.

When the patient was seen 5 months after diagnosis, her visual acuity was stable at 20/20 in each eye. Entrance testing and slit-lamp examination remained unremarkable. A repeat Humphrey Visual Field 30-2 Swedish Interactive Testing Algorithm Fast was performed with the same sequence of right eye, left eye, and then right eye again after dark adaptation. There were high false-negative errors and persistent peripheral defects in both eyes but much improved compared with baseline tests (Figs. 2D to F). The patient reported that she was now capable of navigating at night and was no longer afraid of going outside. She was advised to continue taking the β-carotene supplementation as directed by her endocrinologist and periodically monitor vitamin A levels to prevent nyctalopia symptoms from recurring.

DISCUSSION

Although vitamin A deficiency is a public health concern in the developing world, it is uncommon in developed nations, occurring primarily in patients with liver disease, pancreatic insufficiency, or intestinal malabsorption or in patients who have undergone bariatric surgery.[4,7] Given the rarity of vitamin A deficiency in the United States, other differential diagnoses of nyctalopia should be considered, after first ruling out uncorrected refractive error and cataract. These include retinitis pigmentosa, congenital stationary night blindness, choroideremia, gyrate atrophy, and white dot syndromes. All except the white dot syndromes are hereditary

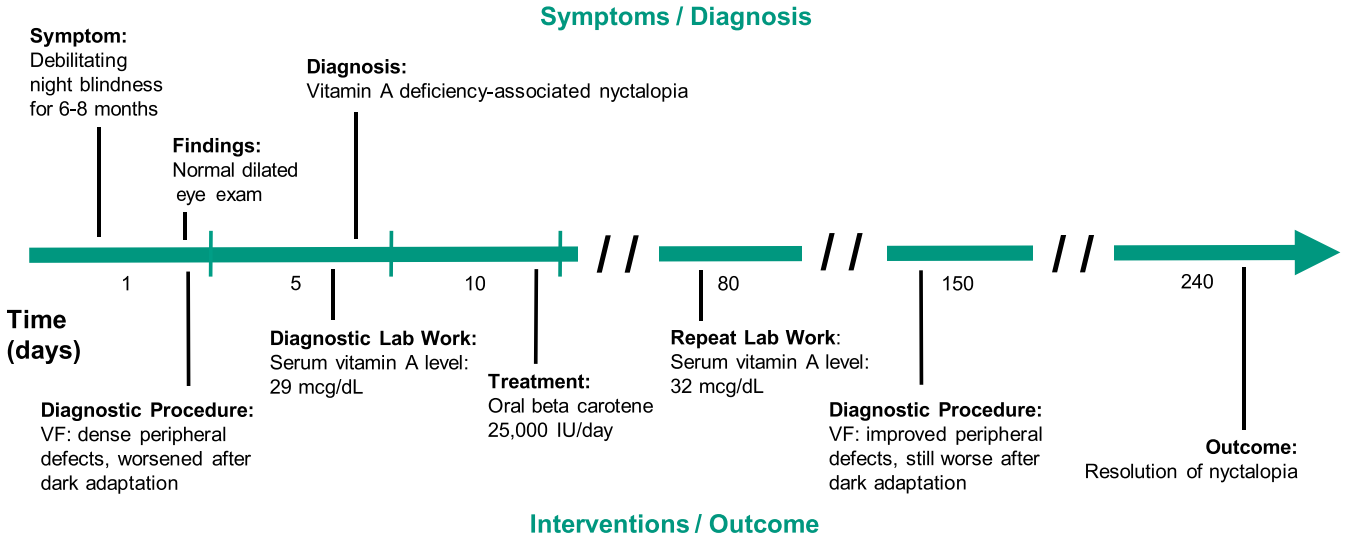

FIGURE 1. Clinical timeline: 64-year-old White woman diagnosed and treated for nyctalopia secondary to severe liver cirrhosis–induced vitamin A deficiency. IU = international units; mcg/Dl = micrograms per deciliter; VF = visual field.

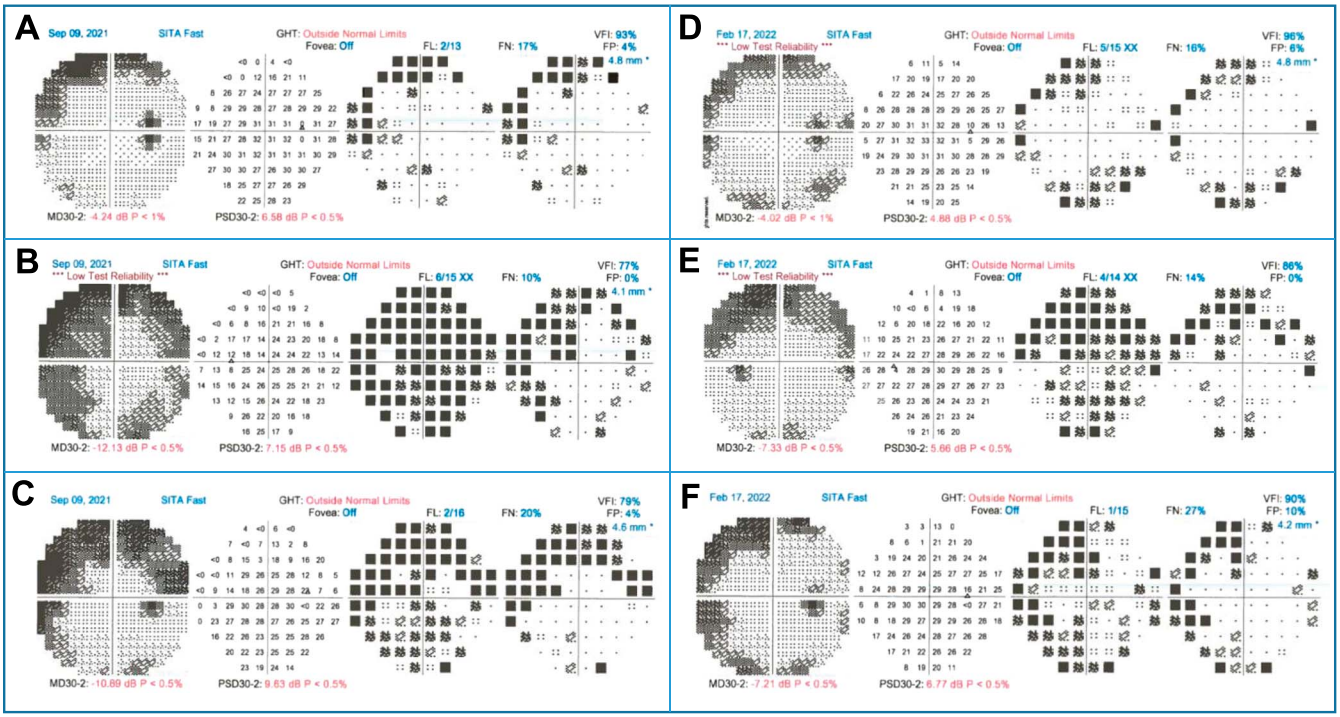

FIGURE 2. Thirty-degree threshold visual field testing, at initial presentation (A–C) and after 5 months of supplementation with oral β-carotene 25,000 IU per day (D–F). (A) Right eye with no dark adaptation. (B) Left eye, after naturally dark adapting for 10 minutes while the right eye performed the test. (C) Right eye, repeated after 23 minutes of dark adaptation, demonstrating denser and deeper defects compared with the initial test. (D) Right eye on treatment with no dark adaptation. (E) Left eye on treatment, after naturally dark adapting for 8 minutes while the right eye performed the test. (F) Right eye on treatment, repeated after 16 minutes of dark adaptation. Both eyes demonstrated improvement from baseline testing, although the right eye peripheral defects still deepened after dark adaptation.

in nature, and nyctalopia usually presents at a younger age.[11–14] White dot syndromes are a unique group of inflammatory chorioretinopathies that share the characteristic appearance of multiple yellow-white lesions located at various layers of the retina, retinal pigment epithelium, choriocapillaris, and the choroid.[15] Given our patient's normal fundoscopic appearance, along with her history of stage 4 nonalcoholic liver cirrhosis, vitamin A deficiency was felt to be the most likely underlying cause of her night blindness. This diagnosis was confirmed by her reduced serum vitamin A level.

The liver plays a crucial role in the absorption and storage of fat-soluble vitamins. It secretes bile, which is vital for the proper absorption of fat-soluble vitamins, as it helps break down lipids in the small intestine.[1] Normally, the liver contains a 2-year supply of vitamin A, mainly in the form of retinyl palmitate ester.[1] Because the abundant storage of vitamin A in the liver can compensate for small deficiencies, symptoms such as nyctalopia are not likely to occur until the later stages of chronic liver disease.[16] A study conducted by Ukleja et al.[17] found that patients with symptoms of night blindness had significantly lower total hepatic vitamin A levels than those without, attesting to the association between liver cirrhosis and nyctalopia secondary to vitamin A deficiency.

Lack of vitamin A can lead to other ocular manifestations as well. Because it is essential for the maintenance of specialized epithelial cells, its absence can cause a wide range of anterior segment findings. Loss of mucous-secreting goblet cells leads to squamous cell metaplasia in the conjunctiva, eventually resulting in xerosis and the formation of Bitot spots, which are triangular, perilimbal plaques that consist of keratinized conjunctival tissue.[2–4] Corneal xerosis and ulceration can also occur and further progress to full-thickness liquefactive necrosis of the cornea, known as keratomalacia, which can cause severe vision loss.[2–4]

Retinal findings in patients with vitamin A deficiency can be variable. Although most present with normal retinas,[5,8,18,19] several case reports have noted numerous punctate white spots in the midperipheral retina with sparing of the macula.[11,20,21] To date, no correlation has been found between the level of serum vitamin A and the presence or absence of retinal lesions. A review of literature indicates that even patients with extremely low levels can have normal fundoscopic findings.[5,8,18,19] Therefore, screening for vitamin A deficiency is indicated in patients with nyctalopia regardless of retinal evidence. Further research is needed to investigate the etiology of the white retinal spots found in some of these patients.

In addition to a detailed case history and a careful review of systems, imaging techniques including OCT, fundus autofluorescence, dark adaptometry, and full-field electroretinography can be helpful in assessing retinal function. Previous reports have noted a mottled pattern of hypoautofluorescence in the macula on fundus autofluorescence and abnormal granular hyperreflectivity of outer retinal bands on OCT, which were not present in this case.[22] Electrophysiological testing was not available in the clinic but would have been helpful in determining the functionality of photoreceptors. Absence of rod responses along with delayed, reduced amplitude of cone responses on electroretinography is indicative of vitamin A deficiency.[22,23] Although the thresholds of both rods and cones may be elevated on dark adaptometry, rods are expected to be affected more severely, as cones are more resistant to damage from vitamin A deficiency.[23] Even though there is no standard

follow-up timeline for patients with nyctalopia secondary to vitamin A deficiency, they should be monitored closely with repeat diagnostic testing to ensure recovery and prevent further ocular complications.

Treatment for vitamin A deficiency is exogenous supplementation. Eye care providers should comanage with primary care providers and/or appropriate specialists when determining the amount of vitamin A supplementation and route of administration. The World Heath Organizaiton recommends 200,000 IU of oral supplementation with β-carotene for 2 days, followed by a repeat course 2 weeks later, for individuals older than 12 years with vitamin A deficiency.[7] However, no standard treatment guidelines have been established specifically for nyctalopia-associated deficiency, as the condition is so infrequently encountered. Resolution of nyctalopia symptoms has been reported with oral, sublingual, intramuscular, and intravenous injections at varying dosages and varying lengths of treatment.[8,10] Although the reference range serves as a guide, the target serum vitamin A level should be individualized for patients who experience symptoms. Depending on severity, recovery of visual function has been reported within a week to a few months after the initiation of treatment. Symptoms can reoccur after tapering or discontinuing vitamin A supplementation; therefore, maintenance therapy is indicated, and serum vitamin A levels should be monitored closely to prevent recurrence.

In summary, although vitamin A deficiency is rare in the United States, it should be suspected in patients who present with complaints of nyctalopia and have a medical history of liver disease or pancreatic insufficiency, or have undergone bariatric surgery. As demonstrated in this case, early diagnosis and appropriate repletion therapy can lead to a recovery of visual function and prevent vision loss.

ARTICLE INFORMATION

Submitted: May 20, 2022

Accepted: October 14, 2022

Funding/Support: None of the authors have reported funding/support.

Conflict of Interest Disclosure: None of the authors have reported a financial conflict of interest.

Author Contributions: Data Curation: SC; Supervision: AJQ; Validation: AJQ; Writing – Original Draft: SC; Writing – Review & Editing: SC, AJQ.

REFERENCES

1. Blaner WS, Li Y, Brun PJ, et al. Vitamin A Absorption, Storage and Mobilization. Subcell Biochem 2016;81: 95–125.

2. Harris EW, Loewenstein JI, Azar D. Vitamin A Deficiency and Its Effects on the Eye. Int Ophthalmol Clin 1998;38:155–61.

3. Gilbert C. The Eye Signs of Vitamin A Deficiency. Community Eye Health 2013;26:66–7.

4. Smith J, Steinemann TL. Vitamin A Deficiency and the Eye. Int Ophthalmol Clin 2000;40:83–91.

5. McBain VA, Egan CA, Pieris SJ, et al. Functional Observations in Vitamin A Deficiency: Diagnosis and Time Course of Recovery. Eye (Lond) 2007;21: 367–76.

6. Stephenson LS, Latham MC, Ottesen EA. Global Malnutrition. Parasitology 2000;121:S5–22.

7. World Health Organization (WHO). Global Prevalence of Vitamin A Deficiency in Populations at Risk 1995–2005: WHO Global Database on Vitamin A Deficiency. 2009. Available at: whqlibdoc.who.int/publications/2009/9789241598019_eng.pdf. Accessed May 1, 2022.

8. Chae T, Foroozan R. Vitamin A Deficiency in Patients with a Remote History of Intestinal Surgery. Br J Ophthalmol 2006;90:955–6.

9. Spits Y, De Laey JJ, Leroy BP. Rapid Recovery of Night Blindness Due to Obesity Surgery after Vitamin A Repletion Therapy. Br J Ophthalmol 2004;88:583–5.

10. Clifford LJ, Turnbull AM, Denning AM. Reversible Night Blindness—A Reminder of the Increasing Importance of Vitamin A Deficiency in the Developed World. J Optom 2013;6:173–4.

11. Ferrari S, Di Iorio E, Barbaro V, et al. Retinitis Pigmentosa: Genes and Disease Mechanisms. Curr Genomics 2011;12:238–49.

12. Zeitz C, Robson AG, Audo I. Congenital Stationary Night Blindness: An Analysis and Update of Genotype-phenotype Correlations and Pathogenic Mechanisms. Prog Retin Eye Res 2015;45:58–110.

13. Pennesi ME, Birch DG, Duncan JL, et al. Choroideremia: Retinal Degeneration with an Unmet Need. Retina 2019; 39:2059–69.

14. Montioli R, Bellezza I, Desbats MA, et al. Deficit of Human Ornithine Aminotransferase in Gyrate Atrophy: Molecular, Cellular, and Clinical Aspects. Biochim Biophys Acta Proteins Proteom 1869;2021:140555.

15. Matsumoto Y, Haen SP, Spaide RF. The White Dot Syndromes. Compr Ophthalmol Update 2007;8:179–200; discussion 203–4.

16. Freund C, Gotthardt DN. Vitamin A Deficiency in Chronic Cholestatic Liver Disease: Is Vitamin A Therapy Beneficial? Liver Int 2017;37:1752–8.

17. Ukleja A, Scolapio JS, McConnell JP, et al. Nutrition Assessment of Serum and Hepatic Vitamin A Levels in Patients with Cirrhosis. JPEN J Parenter Enteral Nutr 2002;26:184–8.

18. De Salvo G, Maguire JI, Lotery AJ. Vitamin A Deficiency–related Retinopathy after Bariatric Surgery. Graefes Arch Clin Exp Ophthalmol 2012;250:941–3.

19. da Rocha Lima B, Pichi F, Lowder CY. Night Blindness and Crohn's Disease. Int Ophthalmol 2014;34: 1141–4.

20. Genead MA, Fishman GA, Lindeman M. Fundus White Spots and Acquired Night Blindness Due to Vitamin A Deficiency. Doc Ophthalmol 2009;119:229–33.

21. Apushkin MA, Fishman GA. Improvement in Visual Function and Fundus Findings for a Patient with Vitamin A–deficient Retinopathy. Retina 2005;25:650–2.

22. Saenz-de-Viteri M, Sádaba LM. Optical Coherence Tomography Assessment before and after Vitamin Supplementation in a Patient with Vitamin A Deficiency: A Case Report and Literature Review. Medicine (Baltimore) 2016;95:6.

23. Lee A, Tran N, Monarrez J, et al. Case Report: Vitamin A Deficiency and Nyctalopia in a Patient with Chronic Pancreatitis. Optom Vis Sci 2019;96:453–8.