Principles and Practice of Clinical Electrophysiology of Vision

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Vitamin A Deficiency

Ronald E. Carr

Night blindness due to vitamin A deficiency has been recognized since ancient Egyptian times, and of the many systemic complications of vitamin A deficiency, the retinal reaction to low vitamin A levels is the best understood. A brief discussion of the metabolism of vitamin A follows to more clearly understand these problems. Vitamin A is transported across the intestinal mucosa and is bound to lipoprotein molecules and then transported and stored in the liver as vitamin A ester. As the body needs vitamin A, these esters are transported as vitamin A alcohol (retinol) to peripheral tissues, including the retina, in conjunction with retinol-binding protein, a transport protein manufactured by the endoplasmic reticulum of the liver. In the retina, vitamin A alcohol is stored in the retinal pigment epithelium and only can be utilized by the photoreceptors after conversion to the aldehyde (retinal). This conversion utilizes the zinc-dependant enzyme alcohol dehydrogenase. Retinal then combines with the protein opsin in darkness to form rhodopsin, and if the retina is bleached by light, this complex breaks down, and the aldehyde is again reduced to the alcohol.

With vitamin A deficiency, as shown in the rat, after the initial stores of vitamin A in the liver and blood have been exhausted, the level of rod visual pigment (rhodopsin) also falls, and reciprocally, the visual threshold rises, thus leading to night blindness.[4]

The classic fundus picture of vitamin A deficiency, first recognized in 1915, is that of scattered multiple white or gray-white spots in the retina, seen mainly in the periphery, with their diameter being that of a retinal vein (Fig 100–1, Plate 22).[11] Such fundus changes are easily separable from other "white-dot" retinal lesions by the finding of a low vitamin A level and the clearing of these lesions with normalization of vitamin A levels.

In recent years small-bowel bypass surgery has been performed for morbid obesity and Crohn's disease, and several reports have been forthcoming that note the development of night blindness, usually several years after surgery.[3, 13] In all cases parenteral vitamin A has alleviated the symptoms.

Electroretinographic (ERG) findings consist of reduced rod and cone responses with normal implicit times.[7] The abnormality of both photoreceptor systems is further borne out by the dark adaptation curves, which show elevation of both rod and cone segments. With psychophysical measurements of dark adaptation, the more peripheral rods respond more quickly than do the perifoveal rods.

Heckenlively (personal communication) has noted in two of his patients with vitamin A deficiency secondary to malabsorption that the photopic and dark-adapted bright-flash ERG waveforms are very similar in shape and timing, quite unlike the usual situation where the dark-adapted bright-flash ERG has larger a- and b-waves as compared with the photopic ERG. Perlman et al. found a similar change in his reported case (Fig 100–2).[7]

Kemp et al.[6] studied visual function and rhodopsin levels in three subjects with vitamin A deficiency secondary to primary biliary cirrhosis and

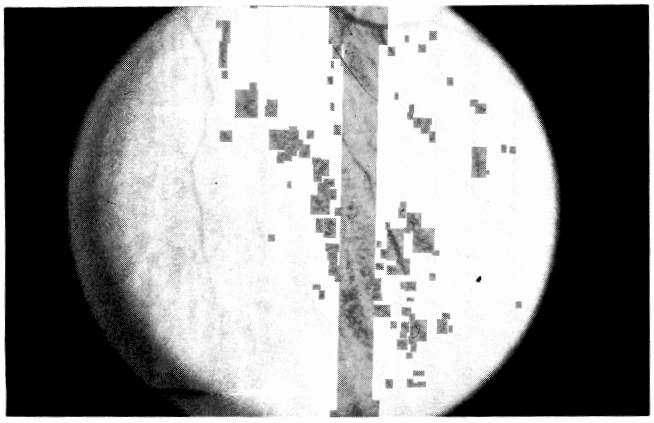

FIG 100–1.
Fundus photograph of a 53-year-old woman with documented vitamin A deficiency from complications secondary to bowel resection in Crohn's disease. Her barely recordable ERG and night vision became normal after parenteral vitamin A and E therapy. (Courtesy of John Heckenlively, M.D.) **(See also Color Plate 22.)**

Crohn's diseases by using two-color adaptometry and fundus reflectometry. Employing green and red targets to test rod and cone dark adaptation thresholds before and after vitamin A supplementation, the authors were able to correlate serum vitamin A levels with cone and rod sensitivity (Fig 100–3). Fundus reflectometry was used in one patient with liver disease to measure rhodopsin levels before and 3 and 9 days after starting vitamin A supplementation; there was complete recovery to normal of rhodopsin, which was correlated with the dark adaptation testing (Fig 100–4).

Abnormalities in liver function have also been associated with vitamin A deficiency and night blindness, possibly due to either abnormal synthesis of retinol-binding protein, lowered serum zinc levels, or simply impaired storage areas for vitamin A esters. Diseases that illustrate these processes include biliary cirrhosis,[12] cystic fibrosis,[8] and chronic alcoholism,[9] the latter presumably with alcoholic cirrhosis. White dots are rarely seen in these conditions and, if present, tend to be more amorphous. Electrophysiological and psychophysical studies in such pa-

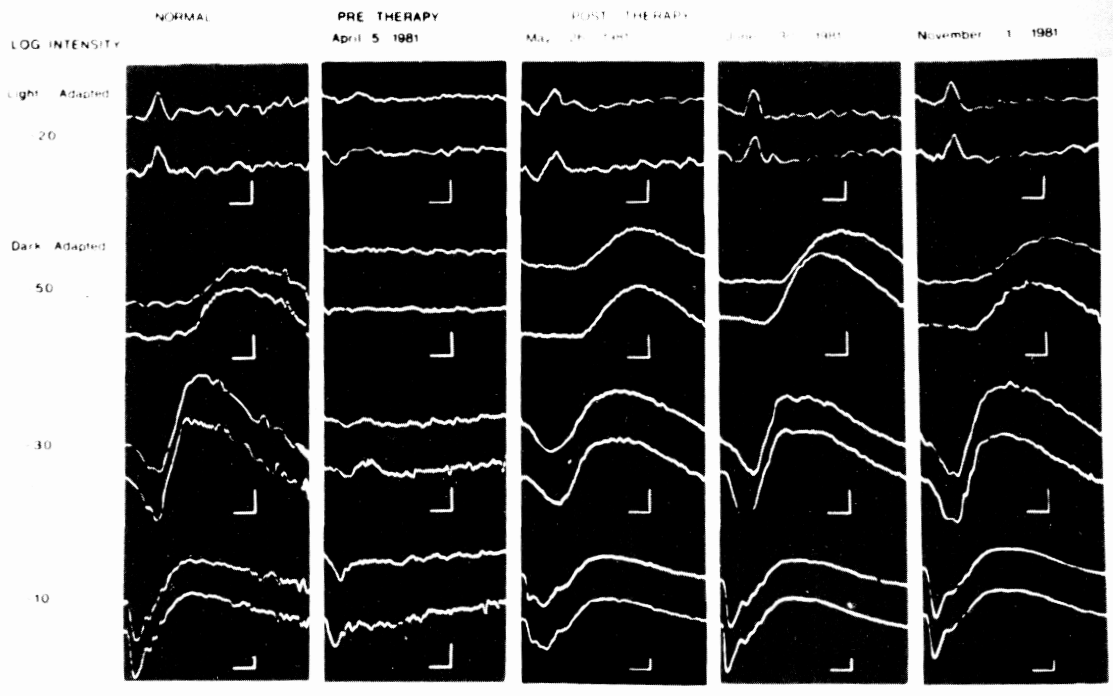

FIG 100–2.
ERGs of a normal subject *(first column)* and a patient with vitamin A malabsorption. The patient's ERG responses were measured at different dates before *(second column)* and after *(third* to *fifth columns)* therapy. The ERG responses were evoked by single white flashes of different intensities during the light- *(1st row)* and dark-adapted states *(second* to *fourth rows).* The intensity of the test light is given as the density of the neutral filter interposed in the light path. The upper tracing is from the left eye and the lower from the right eye. The calibration mark equals 100 μV vertically and 25 ms horizontally. (From Perlman I: *Br J Ophthalmol* 1983; 67:38. Used by permission.)

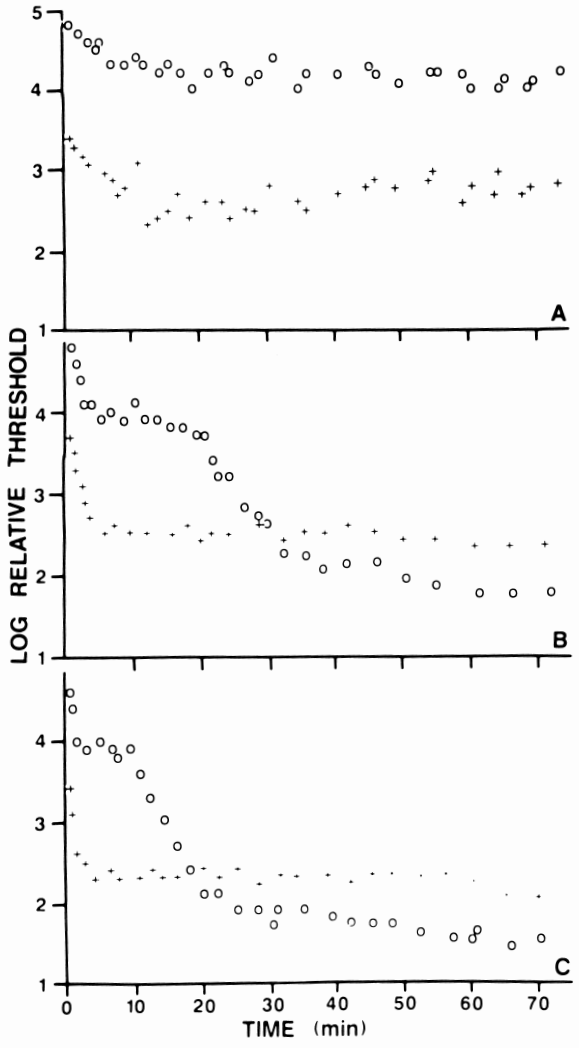

FIG 100–3.
Two-color dark adaptometry of a subject with vitamin A deficiency: relative thresholds to the green *(circles)* and red *(crosses)* stimuli. Measurements were made at a retinal eccentricity of 25 degrees along the horizontal meridian in the nasal field and followed a white bleaching exposure that removed virtually all visual pigment. **A,** results obtained on the first test; **B,** data obtained when vitamin A supplementation had led to partial recovery of visual function; **C,** data obtained when systemic vitamin A levels were normal. (From Kemp et al: *Exp Eye Res* 1988; 46:188. Used by permission.)

tients showed elevated rod and cone thresholds on dark adaptation testing as well as reduced or undetectable rod ERGs with reduced-amplitude cone ERGs and normal implicit times. Full recovery was obtained in virtually all patients following parenteral or oral vitamin A supplements.

The syndrome of abetalipoproteinemia (Bassen-Kornzweig syndrome) is associated with steatorrhea, acanthocytosis, a progressive neuromuscular degeneration, and a generalized degeneration of the retina.[1] In this disorder there is a low level of all fats including the fat-soluble vitamins. The associated absence or near-absence of lipoproteins, among them the lipoproteins responsible for the transport of vitamin A in the blood, is the metabolic abnormality responsible for the concomitant low serum levels of this vitamin. Several studies have shown that some patients given vitamin A with subsequent nor-

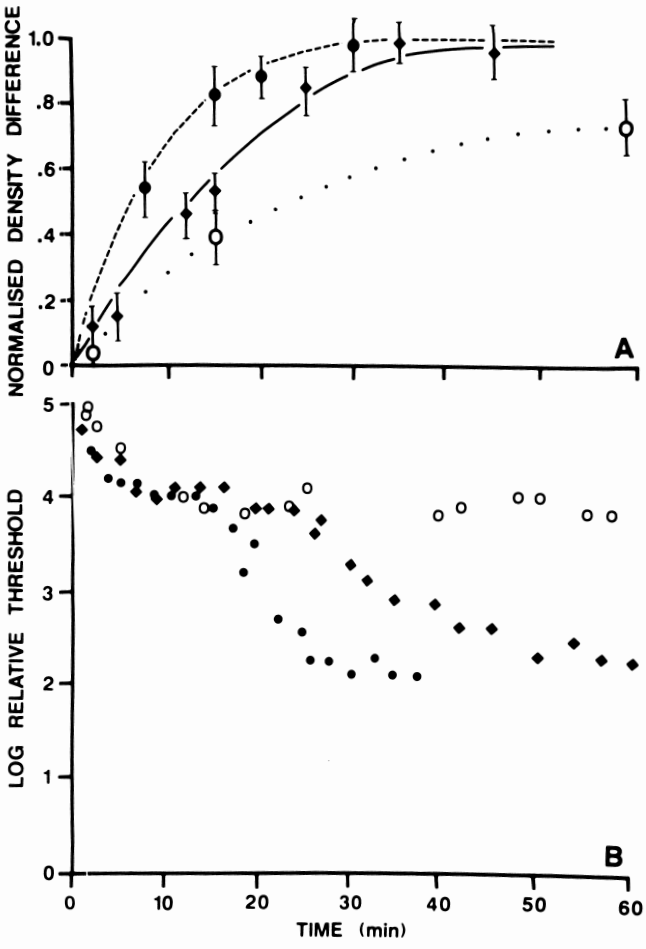

FIG 100–4.
A, Recovery of rhodopsin in a subject with primary bilary cirrhosis and vitamin A deficiency following a full bleaching exposure on days when serum levels were normal *(filled circle)*, mildly abnormal *(diamond)*, and more severely abnormal *(open circle)*. All double-density changes have been normalized to the value obtained at 30 minutes (0 to 0.12 density units) on the day when the serum vitamin A level was normal. Error bars are 1 SD. **B,** corresponding dark adaptometry data for a green stimulus. (From Kemp et al: *Exp Eye Res* 1988; 46:193. Used by permission.)

malization of their vitamin A levels will show an improvement in both dark adaptation as well as the ERG.[5, 10] Bishara et al. suggested that vitamin E should also be administered comcomitantly.[2]

In summary, from a clinical perspective, vitamin A deficiency with subsequent night blindness can occur from a number of diseases affecting different metabolic sites; these include (1) reduced intake of vitamin A and/or carotenoids such as in malnutrition, (2) reduced intestinal absorption of vitamin A such as follows intestinal bypass or resection surgery, (3) defects in the transport of vitamin A as in Bassen-Kornzweig syndrome, and (4) liver disease that leads to abnormalities in the normal vitamin A pathway due to reduced production of retinol-binding protein, reduced amounts of zinc, or reduced storage areas for vitamin A esters.

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