Retinitis pigmentosa in abetalipoproteinemia: Effects of vitamin A

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Two patients with abetalipoproteinemia are shown to develop a serum vitamin A deficiency when maintained on a normal diet. This deficiency leads to a severe impairment of vision, including abnormalities of dark adaptation and the electroretinogram which involve both rod and cone receptor systems. Massive oral doses of vitamin A can reverse these abnormalities. Cone function recovers more rapidly than rod function after vitamin A therapy. The relationship between vitamin A and the retinitis pigmentosa which these patients develop is discussed.

Key words: abetalipoproteinemia, vitamin A, retinitis pigmentosa, rods, cones, dark adaptation, electroretinogram

Retinitis pigmentosa is a retinal abnormality producing blindness accompanied by a characteristic distribution of pigment in the retina and a widespread loss of photoreceptor cells, including both rods and cones. Several genetic and some infectious diseases can produce this type of abnormality. It has been the appearance of the fundus rather than any unique biochemical defect that has placed a variety of retinal diseases into the category of retinitis pigmentosa.

Abnormalities of vitamin A metabolism have often been considered to play a role in inherited forms of retinitis pigmentosa, since this molecule is essential for photoreception and for the structural integrity of visual receptor cells. Until now, however, vitamin A deficiency has never been shown to cause retinitis pigmentosa. There is one report that patients with retinitis pigmentosa tend to have lower-than-normal serum levels of vitamin A. There is another report, however, which was not able to establish such a relationship, and vitamin A therapy has never been able to affect the course of this disease.

In the Bassen-Kornzweig syndrome, a relationship may exist between retinitis pigmentosa and vitamin A. This syndrome, first described in 1950, includes malformed erythrocytes (acanthocytosis), neuromuscular disturbances with ataxia, fat intolerance, and retinitis pigmentosa. In 1958, Jampel and Falls detected a low serum cholesterol in this disease, and in 1960 three independent groups found that the low-density plasma lipoproteins were also reduced. Because of the absence of a specific low-density lipoprotein, Salt and associates called the disease abetalipoproteinemia. The disease involves disturbances of lipid absorption and transport including an inability to form chylomicrons. Consequently, intestinal absorption of vitamin A is im-

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Fig. 1. Case 1. Fundus showing multiple areas of retinal atrophy.

Fig. 2. Case 2. Fundus illustrating the typical bone-corpuscle pigmentation in the midperiphery of the retina.

paired and in addition the absence of beta lipoprotein eliminates the main plasma fraction responsible for carrying carotenoids, the precursors of vitamin A. Therefore, untreated patients with this disease have low serum levels of vitamin A and carotenoids, which alone could lead to retinal degeneration. This paper demonstrates that the vitamin A deficiency these patients develop does produce a severe deterioration of retinal function which can be reversed by vitamin A therapy. It considers the evidence for and against the possibility that the retinitis pigmentosa observed in abetalipoproteinemia is due solely to vitamin A deficiency.

Methods

Two patients, both in their twenties, are presented. One (Case 1) has previously been reported by Mier and associates,15 with history and laboratory data up to 1959. The other (Case 2) has been reported by Kornzweig and Bassen,16 Singer and associates,17 Schwartz and associates,18 and later by Isselbacher and associates,19 with history and laboratory data up to 1964. Our paper is concerned with psychophysical and electrophysiologic measurements of retinal function and their relationship to serum vitamin A levels in these two patients.

Serum vitamin A and carotene were measured by the Carr-Price procedure. Concentrations of less than 20 μg per cent vitamin A in serum were considered abnormal. Vitamin A was administered orally as vitamin A palmitate in doses of 200,000 international units.

Central visual fields were examined on the tangent screen with 1/1000 white and 3/1000 white test objects. Peripheral visual fields were tested at the Goldmann projector perimeter using a 1/4 mm.2 white stimulus at the highest intensity setting.

Visual thresholds were obtained with the Goldmann-Weekers adaptometer, in which an 11 degree spot of white light appears either 8 to 10 degrees above the fovea or in the most sensitive region of the subject's visual field. A continuous record was obtained of the subject's threshold, oscillating above and below the level at which he can just detect the test light. The change in visual threshold in time after a period of light adaptation, i.e., a dark adaptation curve, was determined with the use of an ambient room illumination of 40 footcandles as the adapting light.

Electroretinograms (ERGs) were elicited repeatedly from 1961 to 1964 with a stroboscope subtending 30 degrees of visual angle. Subsequent ERGs were elicited by ganzfeld stimulation with chromatically different lights matched to have identical effects on normal rod vision.

Results

Ocular examination. Fundus examination revealed signs of retinal degeneration in both patients. In Case 1, areas of retinal atrophy without the pigment proliferation of typical retinitis pigmentosa were seen (Fig. 1). This patient's fundus was original-
ly described as having "multiple white dots of varying size" scattered throughout the retina but most profuse in the periphery where they were associated with "irregular dark areas". At this time the authors thought that the pattern resembled retinitis punctata albescens. The white spots are still apparent but the lesions now have an irregular border more suggestive of atrophic retinal changes.

In Case 2, a typical fundus picture of retinitis pigmentosa was seen (Fig. 2). Kornzweig and Bassen followed this patient from age 17 to 22 and described progressive changes in the fundus with narrowing of the arterioles and depigmentation with pigment proliferation at the midperiphery, and this was similar to the appearance of the fundus at the time of his death from cardiac failure at age 27. A histopathologic study of his eyes showed a picture fully compatible with advanced retinitis pigmentosa.

In neither patient was there any ophthalmoscopic evidence of central retinal degeneration as described in the original case of Bassen and Kornzweig and in those of Jampel and Falls and Druez and associates. This is borne out by the normal corrected visual acuity, normal color vision, the absence of a central scotoma, and the histopathologic changes of Case 2, who showed a complete loss of photoreceptors in the retina, except in the macula and between the macula and the temporal margin of the disc where there were cones and a smaller number of rods.

Strabismus and dissociated nystagmus, previously reported by several authors, were also observed in these patients. The onset of symptoms in both patients was in the midteens.

The association of low vitamin A and xerosis is well known, but neither of these patients had any symptoms of xerosis, although the Schirmer test revealed diminished lacrimation in Case 2.

**Visual fields.** Case 1, when described by Mier and associates in 1960, had visual fields which were normal, but the results...
Fig. 4. Dark adaptation final thresholds and serum vitamin A levels in Case 1. Arrows indicate single oral supplements of vitamin A. Normal levels: serum vitamin A, above 20 μg per cent; dark-adapted final threshold, below 3 × 10^2 μAsps.

Fig. 5. Dark-adaptation final thresholds and serum vitamin A levels in Case 2. Arrows indicate single oral supplements of vitamin A.

were considered unreliable because of the patient's inability to cooperate. Fig. 3, A, shows the visual fields in 1970, revealing a ring scotoma in the right eye and a superior arcuate scotoma in the left with full peripheral fields beyond.

Case 2 had visual field examinations when first described in 1957, and subsequently Schwartz and associates reported a composite picture of the visual fields up to 1961. Since that time there had been further loss of field, so that just before the patient's death only small central islands of vision remained in each eye resembling the late stages of retinitis pigmentosa.

Visual thresholds. The thresholds for vision of both patients in the completely dark-adapted state and during the course
of dark adaptation have been studied frequently over a five- to six-year period at the National Institutes of Health. Figs. 4 and 5 show the relationship between visual thresholds in the dark-adapted state and serum vitamin A levels for Cases 1 and 2, respectively, over a period of about two years. In both patients, serum vitamin A levels fell gradually to extremely abnormal levels in between the oral vitamin supplementation. Only after the serum vitamin A levels have remained abnormal for many weeks or months do visual thresholds begin to rise, and then they do so relatively rapidly. The lowest thresholds which Case 1 attained were within normal limits; those of Case 2 were at their best, about 5 to 10 times higher than normal subjects of his age.

Figs. 6 and 7 show the time course of dark adaptation in Cases 1 and 2, respectively, after exposure to an ambient room illumination of 40 footcandles and at a time when their serum vitamin A levels had been low for several months. The time course of adaptation and the final thresh-

Fig. 6. Case 1. Dark adaptation final thresholds and serum vitamin A levels for a three-day period. The dotted line shows the time course of dark adaptation for a normal subject following an initial seven-minute exposure to 2,800 millilamberts. Arrows indicate vitamin A therapy.

Fig. 7. Case 2. Dark adaptation final thresholds and serum vitamin A levels for a ten-day period. The dotted line shows the time course of normal dark adaptation following an initial seven-minute exposure to 2,800 millilamberts. Arrows indicate vitamin A therapy.
CASE 1

PHOTOPIC SCOTOPIC

2/11/62 — — 5.6
8/28/63 — — 33.6
6/5/64 — — 6.9
7/2/64 — — 35.8

CASE 2

PHOTOPIC SCOTOPIC

11/20/61 — — 9.0
8/30/63 — — 62.5
11/4/63 — — 7.6
1/3/64 — — 34.0

Fig. 8. ERG tracings. Dates are at the left and serum vitamin A levels at the right of each trace. Calibration indicates 0.1 sec. horizontally and 0.1 mv. vertically. Positivity up.

old are extremely abnormal in both cases. Case 1 reached the final threshold at about the level at which normal cone thresholds occur and showed none of the great reduction in threshold accompanying normal rod vision. Case 2 was even more abnormal reaching final thresholds, which were 10 times higher than normal cone thresholds and about 10⁵ times higher than normal rod thresholds. Therefore the retinal degeneration in this disease involves both the cone and the rod receptor systems.

After the final thresholds had been attained at 30 minutes, each patient was given 200,000 units of vitamin A orally. In approximately 8 hours the serum vitamin A values of Case 1 rose to normal levels, and this was accompanied by a fall in visual thresholds to within the normal range. The serum vitamin A level of Case 2 rose more slowly after the same dose of vitamin A, and this was associated with a much slower improvement in visual threshold. After 8 days, an additional 200,000 units of vitamin A was given to Case 2, which produced a greater increase in serum vitamin A levels but only a slight additional decrease in visual threshold.

Electroretinography. Fig. 8 shows ERGs and serum vitamin A levels of Cases 1 and 2 obtained at different times over a period of several years. The responses of Case 1 increased considerably when serum vitamin A levels were high, and this was much more apparent in the dark-adapted (scotopic) than in the light-adapted (photopic) response. Fig. 9 demonstrates more clearly that this was due to the large increase in the rod contribution to the ERG. ERGs were never detected in Case 2, indicating the extremely advanced and widespread retinal degeneration he had. Histopathology confirmed this impression by showing the enormous receptor loss in the retinas of both of his eyes.²⁴

Fig. 9 shows the time course of the ERG changes after vitamin A therapy in Case 1 with the use of stimuli which can separate rod from cone function (upper two rows of responses). Before vitamin A supplementation (left column of responses), the amplitude of the ERG was greatly reduced, although a small signal exclusively from the cones (arrow) could be isolated. At 6 hours after vitamin A (middle column), the amplitude of the ERG had increased, but this was due almost entirely to an improvement in cone function (arrow). At 24 hours after vitamin A (right column), there was a large increase in the rod ERG, identified by the responses elicited by lights matched for rod vision (upper two rows). The results again demonstrate that the retinal degeneration in this disease affects both rods and cones and also reveal that rods appear to recover more slowly from vitamin A deficiency than do cones.
Discussion

The results demonstrate that patients with abetalipoproteinemia cannot maintain normal serum vitamin A levels without considerable vitamin A supplementation. The vitamin A deficiency which develops causes a severe abnormality in both visual thresholds and the ERG. These abnormalities can be reversed, and in one of our two patients they were brought within normal limits by high doses of vitamin A. Therefore the vitamin A deficiency which can occur in this disease is fully capable of producing a serious disturbance of retinal function.

In several respects the clinical course of the retinal changes in this condition resembles what would be expected in a retinal deficiency of vitamin A. Rod vision, for example, deteriorates at an earlier stage than does cone vision. This has been observed in human vitamin A deficiency and has been thought to be due to the fact that cone visual pigments are synthesized more rapidly than rod pigments, so that whenever vitamin A is in short supply cones can satisfy their needs more effectively than can rods. There is evidence that rod-cone competition for vitamin A may even be detectable in normal eyes.

The appearance of the fundus in Case 1, the less severely affected of our two patients, also resembles what has been reported in vitamin A deficiency in man. Reports of such cases describe white granules or spots in a row along retinal vessels or coalescing in a clover leaf-like pattern and resembling retinitis punctata albescens. The fundus of Case 1 had white dots scattered throughout the peripheral retina which resembled retinitis albescens. Discrete white spots can still be seen in the peripheral retina (Fig. 1). Other patients with abetalipoproteinemia have also been reported to have had retinal changes resembling a form of retinitis punctata albescens. These patients represent an earlier stage of a retinal degeneration which in Case 2 had progressed to an advanced retinitis pigmentosa.

Pigment proliferation resembling retinitis pigmentosa has never been described in vitamin A deficiency either in man or animals, but retinal changes from prolonged vitamin A deficiency are difficult to produce because of other more deleterious effects of
this deficiency on the organism. It is now known that most of the extraretinal requirements of vitamin A can be satisfied by vitamin A acid, making it possible to determine, perhaps in monkeys, whether prolonged vitamin A deficiency can produce retinitis pigmentosa as implied by these results in abetalipoproteinemia. An answer to this question would be helpful to the understanding of retinitis pigmentosa in general.

There is some evidence against the hypothesis that vitamin A deficiency is responsible for the retinal degeneration in this disease. Several patients have been reported to have developed retinal abnormalities while being maintained on vitamin A therapy from a young age. The patient most completely described was first diagnosed at 18 months of age, at which time the girl's serum vitamin A levels were extremely low. For the next 3 years she was maintained on 6,000 to 8,000 units daily, but this proved to be insufficient to keep serum vitamin A levels normal. When the patient was 4½ years of age, the vitamin A supplementation was increased to 16,000 units daily in order to reach normal serum levels of this vitamin. Therefore, for at least 4½ years of life, this patient had abnormally low serum vitamin A. Although the fundus seems to have been normal during this time, no tests of retinal function were reported. At age 6 the patient's visual thresholds were examined and found to be slightly elevated, and at this time fundus changes were detected which resembled retinitis punctata albescens. It would have been important to know when retinal function became abnormal. In retinitis pigmentosa, retinal function usually fails long before fundus changes appear. In abetalipoproteinemia there is a report of a 6-year-old boy who had no fundus changes but did have an abnormal ERG. It is therefore possible that the vitamin A deficiency which this girl had for 4½ years produced irreversible retinal damage which only later became evident funduscopically.

In order to establish whether vitamin A deficiency alone is responsible for the retinitis pigmentosa in abetalipoproteinemia, it would seem important to maintain serum vitamin A levels normal from the earliest possible age and to use a sensitive index of retinal function such as the ERG to check any evidence of disease. Frequent monitoring of serum vitamin A levels would also seem to be necessary, since there may be fluctuations in the levels of vitamin A reflecting unusual requirements of the vitamin. For example, pregnant women or subjects continuously exposed to bright sunlight develop vitamin A deficiency more rapidly than do normal people.

Another objection to the possibility that vitamin A deficiency alone is responsible for the retinal degeneration in this disease is that, if rods are more sensitive than cones to vitamin A deficiency, then why did some rods remain in the macula of Case 2 when most of the cones in the more peripheral retina were destroyed. Vitamin A demands, however, may not be the same in different regions of the retina. For example, the rod and cone rivalry observed during visual adaptation can best be explained by competition for a similar substrate, possibly vitamin A. This effect can be demonstrated only in certain regions of the retina, presumably where vitamin A demands are greatest. Such a regional difference could also explain why in our patients subjective rod thresholds, which reflect the function of a relatively small portion of retina, improved slightly more rapidly after vitamin A therapy than did the rod ERG, which reflected the rod response of the entire retina.

The results of this study confirm previous work on animals which has shown a close relationship between serum vitamin A, visual thresholds, and the ERG. Most of the previous results have been obtained in rats in which cone vision cannot easily be separated functionally from rod vision. In man, rod vision is affected sooner than cone vision by vitamin A deficiency, although some investigators failed to detect such a difference in monkeys. The vitamin A deficiency produced in these patients

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with abetalipoproteinemia affected rod vision to a much greater extent than cone vision. The ERG is particularly interesting in this regard because rod and cone responses can be clearly isolated from one another.

In conclusion, the evidence suggests that vitamin A deficiency plays a role in the retinal abnormality associated with abetalipoproteinemia. Since the late stages of this abnormality lead to retinitis pigmentosa, it is possible that some other forms of retinitis pigmentosa could also involve defects in vitamin A metabolism.

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