Combined vitamin A and E therapy prevents retinal electrophysiological deterioration in abetalipoproteinaemia

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SUMMARY Eight patients with abetalipoproteinaemia had the typical ocular, systemic, and laboratory findings of this disease. Combined therapy with vitamins A and E was administered, starting as early as the first day of life and as late as 26 years of age. The patients were followed up for 2-6 years. Electroretinography was undertaken in all cases and electrooculography in some. After initiation of vitamin A and E therapy no progression of disturbed visual function could be detected in any patient. These objective tests of retinal function demonstrated that the combined vitamin A and E therapy may be useful in arresting retinal deterioration in abetalipoproteinaemia.

The Bassen-Kornzweig syndrome¹ is a hereditary disorder characterised by gastrointestinal symptoms (steatorrhea), haematological disorders (acanthocytosis), neuromuscular disturbances (ataxia), and retinitis pigmentosa, all appearing in the first decade of life. Early appearance of the retinal disease differs from the hereditary type of isolated retinitis pigmentosa, which appears later, usually during the second or third decade.²

The term abetalipoproteinaemia was given to this disease when it was discovered that lipoproteins containing apoprotein β are absent from the plasma.³⁻⁵ Thus the plasma of these patients contains neither chylomicrons nor very low density lipoproteins (VLDL), nor low density lipoproteins (LDL).^{6,7} Levels of circulating vitamins A and E are very low in all untreated patients.⁸⁻¹¹ Although the reason for the diminished blood levels of these fat-soluble vitamins is not completely understood, it may be a consequence of faulty absorption and subsequent transport as chylomicrons in the lymph to the liver.¹² Normally vitamin A is released from the liver bound to retinol-binding protein and is transported to various tissues as a 1:1 molar complex with serum prealbumin.¹³ Vitamin E is normally transported by

lipoproteins in the plasma.¹⁴ Vitamin A is necessary for the normal operation of the visual cycle, and vitamin E, normally a component of the photoreceptors, plays an essential role in preventing auto-oxidation of polyunsaturated fatty acids.^{15,16}

We have followed a group of 8 abetalipoproteinaemic patients who received vitamin A and E in large doses. The purpose of this study was to determine whether supplementation with both vitamins is effective in arresting retinal deterioration.

Patients and methods

Patients with abetalipoproteinaemia were referred to the Vision Research Laboratory of the Hadassah University Hospital for electrophysiological studies. The diagnosis was based in every case on typical clinical findings, with complete absence of plasma apoprotein β as determined by specific radioimmunoassay. In all patients the plasma cholesterol and triglycerides of the parents were normal, a finding that excludes familial homozygous hypobetalipoproteinaemia.^{12,17}

The electrophysiological studies included:

Electroretinography (ERG). This was done as described in detail elsewhere.¹⁸ In short, the patient is placed in a recumbent position in an electrically

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Table 1 Age, treatment, and ocular findings in 8 patients with abetalipoproteinaemia

Patient no.	Age (years)	Commencement of treatment		Fundus examination	ERG				EOG	
		Vitamin A*	Vitamin E†		First		Last		First	Last
					Age	A wave/ B wave‡	Age (years)	A wave/ B wave‡		
1	1	At birth	At birth	—	1 year	100/320	2	80/300	—	—
2	3	At 10 days of age	At 10 days of age	Normal	7 months	70/290	3	Equal	—	—
3	5	At 4 months	At 4 months	Normal	1½ years	180/410	5	180/400	—	—
4	4	At 18 months	At 20 months	Normal	1½ years	90/280	4	100/300	—	—
5	30	At 26 years ‘irregular’	At 26 years ‘irregular’	Peripapillary chorioretinal atrophy, mild pigmentation in macula, narrow arteries, ‘atypical’ retinitis pigmentosa	26 years	80/180	30	90/200	170%	195%
6	21	At 13 years	At 13 years	Typical retinitis pigmentosa	15 years	15/50	21	15/30	150%	165%
7	11	At 8 years	At 8 years	‘Inverse’ retinitis pigmentosa	10 years	150/250	11	130/250	—	165%
8	27	None§	None§	Pale disc, narrow attenuated arteries, bone corpuscles of pigment, ‘typical’ retinitis pigmentosa	16 years	15/30	27	Extinct	120%	125%

*50 000 U twice a week.

†100 mg/kg/day to a maximum dose of 3000 mg daily.

‡The amplitudes of A and B waves are given in μ V.

§Vitamin A and B were administered for a few days and stopped after the appearance of bilateral papilloedema.

||CT measurements.

shielded cell. The pupils are dilated with tropicamide (Mydriaticum) and neosynephrine 10%, after which contact lenses with corneal electrodes (Henke's type) are fixed to both eyes with methylcellulose 2%. Reference electrodes are fastened to the skin above the eyebrow and a ground electrode is attached to one ear. The stimulating light is positioned 20 cm above and equidistant from both eyes to keep the angle of light comparable to both retinas. The corneal electrodes are connected to the oscilloscope through AC preamplifiers. Thirty minutes are allowed for dark adaptation, and the CT (computer of average transient) is used in cases of very low electroretinograms. With these methods the minimal normal values in our laboratory for adults are 100 μ V for the A wave and 400 μ V for the B wave amplitudes, with a variability between visits of 20 μ V. In normal children the amplitudes are usually lower.

Electro-oculography (EOG). This was performed in older children and adults by the methods of Arden and Kelsey.¹⁹ The 180% light peak/dark trough ratio was considered the lower level of normal.

All patients underwent a routine eye examination including direct and indirect ophthalmoscopy. Blood samples were taken to determine the vitamin A and E levels in the serum.

Results

Table 1 summarises the main clinical and electrophysiological findings in the 8 patients who were included in the study, while Fig. 1 shows serial changes in each patient as detected during the period of follow-up. Three subgroups were noted. The first included 4 children (cases 1-4) who started combined vitamin A and E therapy during the first 2 years of life. ERG values and normal fundus picture did not change till their present ages of 2, 3, 5, and 4 years respectively. The reduced ERG values of case 4 on his second examination (Fig. 1) were due to technical reasons, as proved by 2 additional examinations. Repeated tests showed serum vitamin E levels to be between 0.15 and 0.2 μ g/ml (normal range 0.5-0.8 μ g/ml), or about one-third of the normal values.* Vitamin A levels were between 13 and 45 μ g/100 ml (normal range 15-60 μ g/100 ml). (SI conversion: μ g/ml = mg/l; μ g/100 ml $\times$ 0.01 = mg/dl.)

The second subgroup consists of 3 adults (cases 5-7) who started the vitamin A and E treatment later in life, only after electrophysiological functions were already much reduced, and the fundi showed changes of retinitis pigmentosa of different stages of severity. All 3 patients maintained a stable ERG and EOG

Combined vitamin A and E therapy

Fig. 1 Serial electroretinogram of B wave amplitudes in patients with abetalipoproteinaemia after initiation of combined vitamin A and E therapy. Patient 8 did not receive sustained therapy.

after initiation of therapy. The vitamin E serum level remains around $0.15 \mu\text{g/ml}$ and vitamin A ranged between 22 and $49 \mu\text{g}/100 \text{ ml}$.

Patient 8 formed a subgroup on her own in that the ERG was reduced and the retinal pathology progressed during the period of observation. However, this patient received treatment for a few days only, stopping after the appearance of bilateral papilloedema, a rare but known complication of vitamin A therapy. Vitamin E levels in the serum of this patient were found to be $0.03 \mu\text{g/ml}$ only, while that of vitamin A amounted to $22 \mu\text{g}/100 \text{ ml}$.

*Because in an abetalipoprotein carrier lipoproteins for vitamin E are much reduced, only one-third of normal plasma levels can be reached even with optimal therapy.²⁰

Discussion

Since Bassen and Kornzweig¹ reported their first case of abetalipoproteinaemia in 1950 only 36 cases had been described until 1976.⁹ The present study deals with 8 additional patients. The results indicate that in

abetalipoproteinaemia combined vitamin A and E therapy has a 'stabilising' effect in preventing deterioration both in the fundus and in the electrophysiological functions of the retina. Is this 'stabilising' effect the result of each vitamin acting separately, or is it due to their combined mode of action?

Patients with abetalipoproteinaemia have been treated by vitamin A^{11 21 22} and vitamin E.^{10 20} Sperling *et al.*¹¹ claimed that vitamin A is effective if administered before the retinal changes become irreversible. However, they reported a follow-up for only 3 months. Müller *et al.*²³ described a patient who developed the typical retinal changes at the age of 5 years in spite of being treated with vitamin A and having normal serum levels of this vitamin since the age of 12 months. Similarly Wolff *et al.*²¹ reported that vitamin A supplementation in their patients did not prevent the development of retinitis pigmentosa. Thus it seems that vitamin A offers only temporary benefit to these patients. The effect of vitamin E was studied by Müller *et al.*¹⁰ and Azizi *et al.*,²⁰ and a long-lasting beneficial effect was suggested but not proved.¹²

Interrelationships of vitamins A and E on retinal structure and histology have recently been demonstrated experimentally by Robinson and coworkers.²⁴ While vitamin A is specifically essential in the visual cycle, vitamin E is known to have broader functions. It not only protects a variety of cellular membranes—including the retinal photoreceptors—from auto-oxidation, it may in addition serve as an antioxidant for vitamin A *per se*. A combined deficiency of both vitamins was shown to accelerate the retinal degeneration in experimental animals,²⁴ findings which provide a basis for understanding the possible pathogenesis of the pigmentary retinopathy in untreated patients with abetalipoproteinaemia. Our observations in the 8 patients presented here indicate a synergistic or complementary effect of the 2 vitamins. Accordingly the simultaneous administration of vitamins A and E in patients suffering from abetalipoproteinaemia is advocated.

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