

Arrest of neuropathy and myopathy in abetalipoproteinemia with high-dose vitamin E therapy

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A 16-year-old girl, one of dizygotic twins, presented in 1976 complaining of a 1-year history of a lack of coordination and an inability to run. The results of biochemical tests confirmed the diagnosis of classic abetalipoproteinemia. In addition to the recognized neurologic features of this disorder, she had a reduced evoked motor unit potential and markedly elevated serum levels of muscle enzymes, which suggested myositis. The serum vitamin E level was markedly decreased. Oral therapy with vitamin E, 800 mg daily, was begun, and in 1981 the dosage was increased to 3200 mg daily. Over the 7 years of follow-up she improved clinically, there was an increase in the evoked motor unit potential, the serum levels of some of the muscle enzymes decreased to normal, and the serum and tissue vitamin E levels increased significantly. It was concluded that treatment with high doses of vitamin E was responsible for the arrest of the usually progressive neuropathy and myopathy.

En 1976 une jumelle biovulaire âgée de 16 ans se présentait pour incoordination motrice et incapacité de courir évoluant depuis 1 an. Les trouvailles biochimiques étaient celles d'une abétalipoprotéïnémie classique. En plus des signes neurologiques reconnus de cette maladie, on observait une diminution du potentiel évoqué d'une unité motrice, une forte augmentation des taux sériques des enzymes musculaires, ce qui suggérait une myosite, et un abaisse-

ment marqué de la concentration sérique de la vitamine E. On entreprenait alors un traitement vitaminé E à la dose quotidienne de 800 mg par voie buccale, dose qui devait être portée à 3200 mg par jour en 1981. Sur les 7 années d'observation on note une amélioration clinique, le relèvement du potentiel évoqué de la même unité motrice, la normalisation du taux de certains enzymes musculaires et une augmentation significative de la concentration tissulaire et sérique de la vitamine E. Le tout permet de conclure que l'administration de celle-ci à hautes doses a arrêté l'aggravation d'une neuropathie et d'une myopathie qui sont habituellement évolutives.

Abetalipoproteinemia is a biochemical deficiency caused by the absence of apoprotein B, which is essential for the transport of lipids in the liver and the mucosa of the small intestine. The resulting low plasma levels of chylomicrons and of low-density and very-low-density lipoproteins (LDL and VLDL) are associated with low levels of fat-soluble vitamins, particularly vitamin E, and a

clinical syndrome of ataxia, acanthocytosis, atypical retinitis pigmentosa, fat malabsorption, and low plasma triglyceride and serum cholesterol levels.¹⁻³ The neurologic deficit is usually progressive. We describe a patient with abetalipoproteinemia, one of dizygotic twins, in whom oral therapy with high doses of vitamin E resulted in an arrest of the neuropathy and myopathy.

Case report

A 16-year-old girl presented in 1976 with a 1-year history of incoordination and an inability to run. She was one of dizygotic twins born at term. Her parents were normolipoproteinemic and nonconsanguineous. As an infant she had had diarrhea, which had abated with the institution of a low-fat diet. At age 8 she began to complain of decreased night vision. At age 11 she was found to have acanthocytosis and very low serum cholesterol and plasma triglyceride levels. Abetalipoproteinemia was suspected, and she was treated orally with vitamin A, 25 000 IU daily. She remained

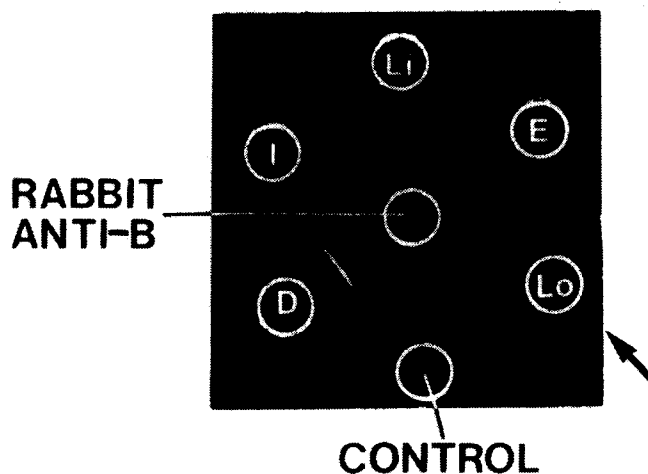


Fig. 1—Results of radial immunodiffusion testing of plasma from family members and from a known healthy control against rabbit antiapoprotein B. Absence of immunologic precipitation with patient's plasma (arrow) and identical lines of precipitation with all other plasma samples indicates absence of apoprotein B from patient's plasma, which is pathognomonic of abetalipoproteinemia.

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asymptomatic, although her academic performance was poor and she was short. At age 15 she had a normal menarche. She first experienced difficulty with balance and generalized weakness at age 16.

At the time of presentation her height and weight were 148 cm and 40 kg respectively (both below the third percentile for her age). She had crowded dentition, a high, arched palate, pectus excavatum and mild kyphoscoliosis. The thyroid gland, heart, lungs, abdomen and genitalia were normal. She had small, glandular breasts.

Neurologic examination revealed that she was mildly dysarthric. She had normal visual acuity but hyperpigmentation of the inferior aspect of both retinæ. The function of the cranial nerves was normal. She had a diffuse decrease in muscle bulk, bilateral pes cavus and bilateral hallux valgus. All muscle stretch reflexes were absent, and the plantar reflexes were upgoing. Pinprick sensation below both knees was significantly decreased, and there was a loss of proprioception and vibration in a glove-and-stocking distribution. She had symmetric weakness of the proximal muscles, a mild intention tremor and dysdiadochokinesia of both arms and legs. Romberg's sign was present, and she had a wide-based steppage gait. Her intelligence quotient was 87.

The hemoglobin concentration was 127 g/L, the leukocyte count $5.5 \times 10^9/L$, with a normal differential, and the platelet count $250 \times 10^9/L$. A peripheral blood smear showed ancanthocytosis with 3% reticulocytes. The prothrombin time and activated partial thromboplastin time were within control limits. The serum electrolyte, blood urea nitrogen, serum creatinine and plasma glucose levels were normal, as were the serum calcium, phosphorus, magnesium, folic acid and vitamin B₁₂ levels.

The plasma triglyceride and serum cholesterol levels were decreased, at 0.10 mmol/L (normal, 0.60 to 1.80 mmol/L) and 1.8 mmol/L (normal, 3.0 to 7.0 mmol/L) respectively. Lipoprotein electrophoresis showed an absence of LDL and VLDL from the plasma. The diagnosis of abetalipoproteinemia was confirmed by radial

immunodiffusion testing of plasma from the patient and from healthy controls against rabbit antiapo-protein B (Fig. 1).

The serum creatine kinase, glutamic oxaloacetic transaminase (SGOT) and hydroxybutyrate dehydrogenase (HBDH) levels were elevated (Table I).

Conduction velocities in the right peroneal and the right posterior tibial nerves were within normal limits; however, the evoked motor unit potential of the right extensor digitorum brevis was markedly reduced (Fig. 2). Electron microscopy of a specimen of the sural nerve showed

atrophy and a relative decrease in the number of large myelinated axons (Fig. 3). A biopsy specimen of the tibialis anterior muscle showed some areas of fibre shrinkage, with nuclear clumping.

The plasma and erythrocyte vitamin E levels were low (Table II). In 1977 treatment with d- α -tocopherol acetate, 800 mg/d, was begun. Therapy with vitamin A, 25 000 IU/d, and vitamin K, 5 mg/d, was continued and her diet was not restricted. Clinical and laboratory reassessments were done at regular intervals after the initiation of vitamin E therapy. In 1981 the daily dose of

Table I—Serum levels of muscle enzymes in a patient with abetalipoproteinemia

Serum enzyme	Year; level (U/L)				Normal values (U/L)
	1976	1979	1981	1983	
Creatine kinase	314	42	37	40	10–45
Glutamic oxaloacetic transaminase	97	45	52	48	15–60
Hydroxybutyrate dehydrogenase	356	267	314	303	50–145

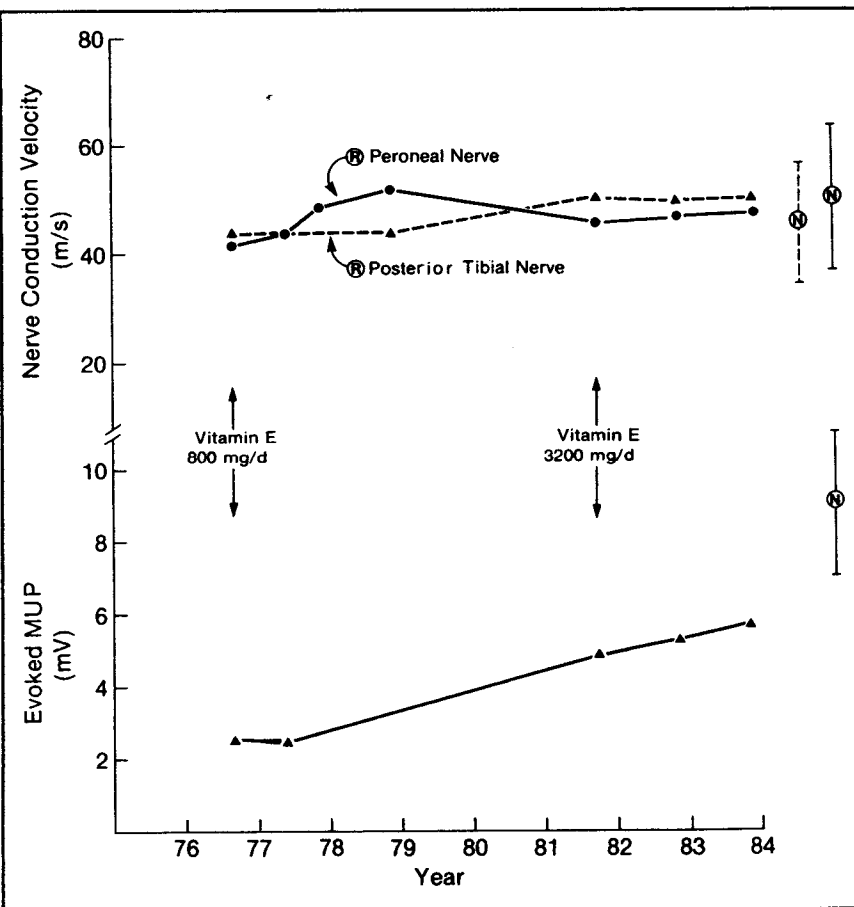


Fig. 2—Conduction velocities of right peroneal and right posterior tibial nerves, and evoked motor unit potential (MUP) of right extensor digitorum brevis plotted against time. Over 7 years, nerve conduction velocities remained within normal (N) limits and evoked MUPs remained abnormally low, although they increased with time.

vitamin E was increased to 3200 mg in view of her objective improvement.

She underwent extensive evaluation in 1983. Her condition had improved over the 7 years, and she was now able to run and rollerskate. Her strength in the proximal muscles had returned to normal, the tremor and dysidiadochokinesia had lessened, and her gait had improved.

Three percent of the cells in the peripheral blood smear were still

acanthocytes and reticulocytes. The remainder of the hematologic and biochemical findings were unchanged, with the exception of the serum creatine kinase and SGOT levels, which had returned to normal (Table I). Over the 7 years the nerve conduction velocities had remained within normal limits, but the evoked motor unit potential of the right extensor digitorum brevis had increased, though it remained abnormally low. There was an increase

in the plasma and erythrocyte vitamin E levels, although not to normal limits (Table II). The vitamin E level in subcapsular adipose tissue was 331 μmol per milligram of triglyceride. This value is below normal but is higher than expected for untreated patients with abetalipoproteinemia,⁴ in whom it is usually undetectable.

Discussion

Abetalipoproteinemia is presumed to be inherited as an autosomal recessive trait.² This is the first report of abetalipoproteinemia in twins. As they were dizygotic, it is unlikely that the disease was acquired through some stress during the intrauterine period. The existence of some form of heritable predisposition is thus confirmed.

Our patient had clinical signs of abnormal cerebellar, posterior column and peripheral nerve function. These signs are consistent with those of the classic neurologic syndrome of abetalipoproteinemia^{2,5} but are also similar to those of neurologic syndromes in children with biliary atresia,^{6,7} cholestatic liver disease^{6,7} and cystic fibrosis.^{7,8} Biochemically these conditions are all associated with very low serum vitamin E levels, probably as a result of fat malabsorption.

Studies of vitamin-E-deficient rats⁹ and growing Rhesus monkeys¹⁰ detected clinical and neuropathological features analogous to those found in conditions associated with vitamin E deficiency in humans.⁷⁻⁹ Furthermore, supplementation of the diet with vitamin E resulted in a delay of progression of the neurologic lesions in the animals,^{9,10} in some humans with neuropathy due to abetalipoproteinemia¹¹⁻¹³ and in children with cholestatic neuropathy.⁸ Our patient improved subjectively and objectively after 7 years of oral therapy with vitamin E.

Vitamin-E-deficient states are associated with microscopic myopathy.^{10,14,15} The myopathy of abetalipoproteinemia is complex, being related to both denervation and intrinsic myositis. There has been no report on the effect of vitamin E supplementation on abetalipoproteinemia myopathy. In our patient the return to normal of the serum muscle en-

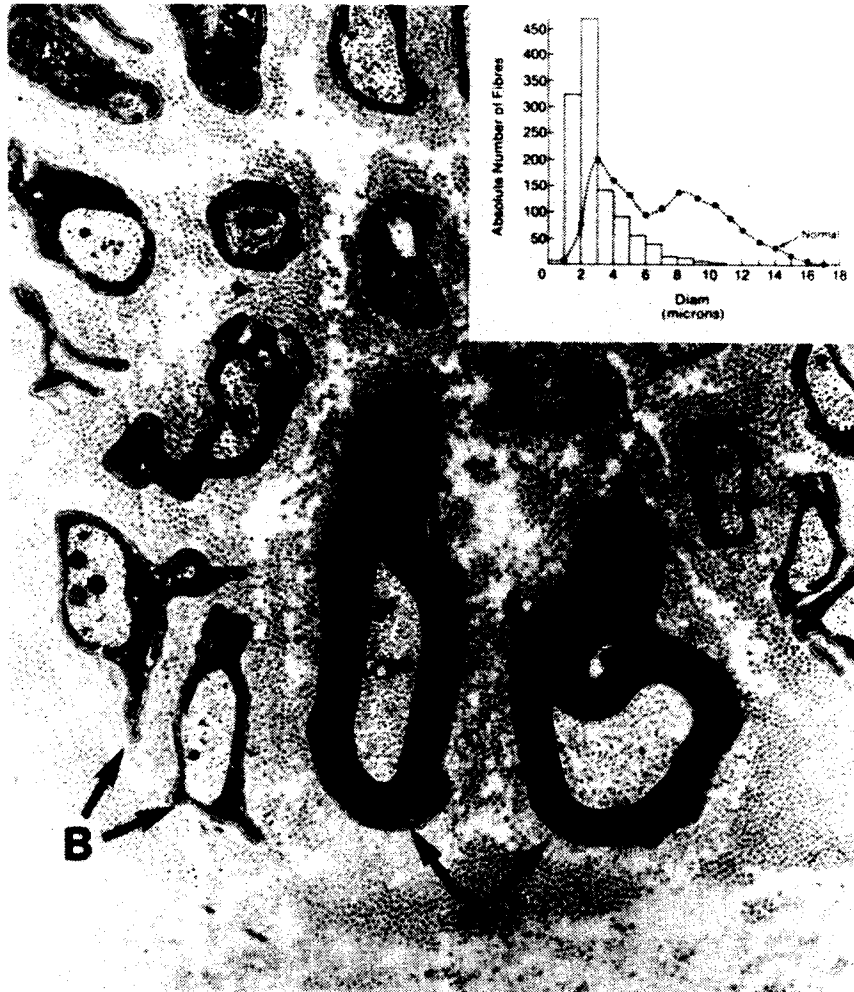


Fig. 3—Electron micrograph of sural nerve specimen shows atrophy of myelinated axons (A) and redundant membrane of nonmyelinated axons (B). Inset: histogram analysis of nerve fibres reveals absolute and relative deficiency of large myelinated axons, with loss of normal bimodal distribution in patients of this age.

Variable	Year; level		Normal values
	1976*	1983	
Plasma, $\mu\text{mol/L}$	0.14	6.04	11.6–46.4
Erythrocytes, $\mu\text{mol/L}$	0.5	1.8	3.4–4.1
Adipose tissue, $\mu\text{mol/L}$	ND	331	460–690

*ND = not done.

zyme levels associated with clinical improvement and an increase in the plasma vitamin E levels may indicate a beneficial effect of vitamin E on the neuropathy of abetalipoproteinemia. The persistently elevated serum HBDH level was probably due to continuing hemolysis of the acanthocytes.

Vitamin E plays an as yet undefined role in neuromuscular function. However, evidence indicates that it stabilizes biologic membranes.¹⁶ A prolonged deficiency of vitamin E is associated with the fairly late onset of neuromuscular symptoms in abetalipoproteinemia^{11,12,17} and in some vitamin-E-deficient states.^{4,7-9} Other investigators have shown that the decreased serum and tissue vitamin E levels in patients with this disorder can be increased, although not to normal, with high-dose oral vitamin E therapy.^{17,18} However, recent data suggest that as indicators of vitamin E status, serum vitamin E levels are less reliable than tissue vitamin E levels.¹⁹

The efficacy of the oral administration of high doses of vitamin E may be due to a functional increase in fat absorption through the portal vein, a pathway that does not depend on lipoprotein synthesis.

In summary, vitamin E supplementation, with a subsequent increase in serum and tissue vitamin E levels, appeared to arrest the neuropathic and myopathic progression of abetalipoproteinemia in our patient. Therefore, early detection of this disorder, together with high-dose vi-

tamin E therapy and monitoring of vitamin E levels at regular intervals, may arrest and, indeed, prevent the debilitating neuropathy and myopathy associated with abetalipoproteinemia.

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