Case Report

Reversible neurological symptoms caused by vitamin E deficiency in a patient with short bowel syndrome[1-3]

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ABSTRACT The effect of vitamin E deprivation on the fully developed human nervous system is not known. In children with fat malabsorption from various causes neuropathological and neurological changes have been ascribed to vitamin E deficiency. Herein we described a neurological deficit that occurred in a 64-yr-old man with chronic steatorrhea leading to severe vitamin E deficiency. Long-term supplementation with vitamin E resulted in clinical improvement beginning a few months after normalization of his vitamin E status. *Am J Clin Nutr* 1982;36:1243–1249.

KEY WORDS Vitamin E deficiency, neurological deficit, response to supplementation

Introduction

Pathological changes in the CNS can readily be produced in animals subjected to vitamin E-deficient diets. The most pronounced changes have been degeneration of the posterior columns (1). In man, the role of the vitamin in neurological diseases is uncertain. Dystrophic axons in the gracile and cuneate nuclei of the medulla have been described in children with cystic fibrosis (2, 3) and biliary atresia (4), diseases in which vitamin E deficiency is a common finding. Neurological manifestations caused by vitamin E deficiency have not been demonstrated with certainty, however, several recent case reports suggests such a relationship (4–8). This report describes a 64-yr-old man with chronic steatorrhea, resulting in prolonged vitamin E deficiency, who developed ataxia and a visual field defect that corrected with 2 yr of vitamin E supplementation.

Case report

A 64-yr-old man had a 25-yr history of Crohn's disease involving multiple bowel resections for fistulae and obstruction. His last operation, in 1970, left him with 30 cm of jejunum anastomosed to the transverse colon, since then he has experienced frequent abdominal cramps and 4 to 8 stools daily. He was managed on a low fat diet with medium-chain triglyceride, multivitamin, iron, calcium and magnesium oral supplements; and intramuscular vitamin A 50,000 IU weekly, vitamin K 10 mg and vitamin B_{12} 1000 μg/month, and vitamin D in oil 500,000 IU every 2 months. In 1970 he was 10% underweight (9) (45 kg, height 158 cm) and by 1978 he had dropped to 30% underweight (35 kg). In 1974 he first noted some unsteadiness with walking and by 1977 he was unable to walk without a cane. In May 1978, when he was first referred to the Albany Medical College Clinical Nutrition Program, he was unable to walk even a few steps without assistance and had noticed increased difficulty seeing, especially in dim light. The patient was admitted to hospital for insertion of a silastic central line and education about the technique of home parenteral nutrition. **Table 1** shows the composition of his nutrient solution. On initial physical examination the abnormal findings were marked cachexia, pigmentary degeneration of the retina, similar to the appearance of retinitis pigmentosa, and massive bilateral visual field scotomata preserving only 10% of central vision (**Fig 1**). As shown

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TABLE 1
Average daily parenteral nutrient intake

Macronutrients	
Fluid (ml)	3000
Amino acids (g)	127.5
Calories (kcal)	3000
Sodium (mEq)	105
Potassium (mEq)	90
Magnesium (mEq)	15
Calcium (mEq)	15
Chloride (mEq)	105
Phosphorus (mg)	1300
Trace elements*	
Zinc (mg)	5
Copper (mg)	1.6
Chromium (μg)	2
Iodine (μg)	120
Selenium (μg)	120
Vitamins	
A (IU)	3000
D (IU)	300
E (mg)†	2.2
K (mg)	1.5
C (mg)	150
B_1 (mg)	1.5
B_2 (mg)	3.0
Niacin (mg)	30
B_6 (mg)	4.5
Pantothenate (mg)	7.5
Biotin (μg)	60
Folate (μg)	600
B_{12} (μg)	30
Essential fatty acids	
Linoleic acid (g)	7
Linoleic acid (g)	1

* Iron was given as oral ferrous sulphate 440 mg daily.

† Coming largely from a combination of the multivitamin preparation (5 ml MVI conc USV Pharmaceuticals, twice weekly = 10 mg *dl* α tocopherol/wk) and intravenous fat solution (500 ml 10% Intralipid Cutter Laboratories, twice weekly = 6 mg tocopherol/wk 5% α tocopherol, 95% racemic forms of γ tocoperol).

in **Figure 2** he had generalized motor weakness, greater in proximal than distal muscle groups, a broad based gait with marked ataxia on turns and stops, brisk reflexes, and a bilateral Babinski response. Proprioception was moderately diminished in all extremities. Laboratory studies drawn prior to initiating intravenous nutrition and two weeks after any intramuscular vitamin injections, were as follows: Hb 10.3 g/dl, hematocrit 31.3%, normal red cell indicies but moderate hypochromia on blood smear, reticulocyte count 1.8%, leucocyte count 4,100/cu mm (6% lymphocytes), platelets 130,000/cu mm, serum iron 38 μg/dl, total iron binding capacity 364 μg/dl, total serum protein 5.9 g/dl, albumin fraction 3.1 g/dl, cholesterol 130 mg/dl, and fasting triglycerides 63 mg/dl, plasma zinc 45 μg/dl (normal 70 to 120 μg/dl), plasma copper 76 μg/dl (normal 90 to 130 μg/dl), serum carotene 0.3 μg/dl (normal > 80 μg/dl), serum vitamin E (10) 0.03 mg/dl (normal 0.8 to 1.2 mg/dl) and in vitro peroxide hemolysis 100% (normal < 10%) (11). All other values were normal including serum electrolytes, magnesium, calcium, liver enzymes, total bilirubin, CPK, prothrombin time, vitamin A, B_1, B_2, B_6, niacin, folic acid, B_{12}, stools for occult blood, an electrocardiogram, chest x-ray, electromyography, and peripheral motor and sensory nerve conduction velocities. His plasma fatty acid pattern showed a normal triene:tetraene ratio (10) but a reduced amount of linoleic acid (18:2–8.6, 20:3–0.8, 20:4–5.2 expressed as percentage of total lipid). Muscle biopsy showed some atrophy of type II fibers. Electroretinography revealed marked decrease of the A and B wave amplitudes, under both scotopic and photopic conditions (eg, right eye, using maximal standard stimulus under dark adaption: A wave 20 uv, normal 50 to 150 uv; B wave 30 uv, normal 300 to 400 uv) and an increased latency of response. Cervical spine x-ray, CT scan of the brain, and cerebropsinal fluid examination were normal.

After parenteral nutrition was instituted the patient's plasma zinc and serum albumin rapidly corrected, he started to gain weight and strength and after 8 wk he was 49 kg and strong enough to be discharged to continue his infusions at home. For 2 months postdischarge the intravenous fat emulsion was doubled to 2 l of 10% Intralipid/wk. His plasma linoleic acid level increased to 11.0%, still below normal values which in our laboratory are 35.5 ± SE 2.3. By August 1978 the patient had reached his ideal weight of 51 kg and, as shown in Figure 2, his weight has fluctuated no more than 2 kg ever since. Despite his obvious recovery from protein calorie malnutrition, there was no immediate improvement in his gait ataxia and visual disturbance, and 9 months after parenteral nutrition was initiated a neurological reassessment was essentially unchanged except for some improvement in muscle strength. At this point conduction in the central sensory pathways was assessed by visual and somatosensory evoked potentials, using a black and white checkerboard pattern and an electrical stimulus to the median nerve at the wrist (**Fig 3**). (References 13 and 14 provide a detailed description of these tests.) Our patient's visual evoked potential latencies were normal but the electrical impulses applied to the wrist were conducted normally to the brachial plexus and dorsal columns, but were markedly delayed in arriving at the contralateral parietal cortex. This conduction delay indicated a defect in the primary somatosensory pathways. The parenteral nutrient solution supplied approximately 2.2 mg of tocopherol/day (the source and biological form are given in Table 1). As shown in Figure 2, 2 months after discharge the patient's serum vitamin E was still very low (0.15 mg/dl) and his peroxide hemolysis remained at 100%. At that point an attempt was made to correct his vitamin E status with 3200 mg of intramuscular *dl* α tocopherol acetate in sesame oil (E-Ferol-O'Neal, Jones and Feldman Pharmaceutical). Four weeks later his serum vitamin E was 0.24 mg/dl and his peroxide hemolysis was 70%. This slight improvement was not sustained. In late October 1978 oral supplementation was started with 200 mg/day of water miscible *dl* α tocopherol acetate in two divided doses (Aquasol E—USV Pharmaceutical). In the next 9 months our patient's vitamin E status eventually normalized and during this same period he noted a gradual improvement in his vision and gait. A neurological reassessment in November 1979 showed objective improvement of both his visual fields (Fig 1) and gait disturbance (Fig 2). This improvement continued and 2 yr after starting aggressive vitamin E repletion, the patient felt

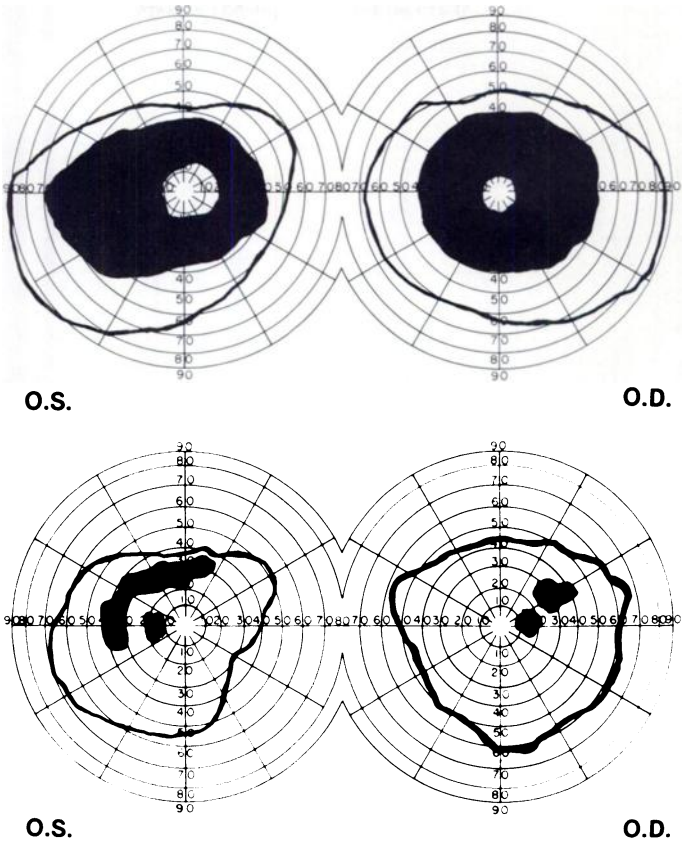

FIG. 1. The patient's visual fields in May 1978 (*top*) and December 1979 (*bottom*). The isopters plotted and scotomas shown are to the largest and brightest test target. OS = left eye, OD = right eye.

he was back to normal. Neurological reassessment in October 1980 revealed only minimal gait disturbance. Repeat electroretinograms showed a doubling of the A wave amplitude (20 → 45 uv), however, this was still subnormal (normal 50 to 150 uv) and there was no change in the B wave. The delay is somatosensory conduction persisted, as did the depressed linoleic acid levels (18:2–12.3%).

Discussion

Although there is no general agreement about the physiological function of vitamin E, its primary role is believed to be its antioxidant effect, protecting unsaturated lipids in cellular membranes from free radical oxidation damage (15, 16). It may also have a structural role in biological membranes, interacting with the membrane phospholipids and possibly forming a complex with the arachidonic acid component (17).

Animal experiments have clearly demonstrated that vitamin E deficiency will result in a wide array of pathological abnormalities, including hemolytic anemia and neurological manifestations (18). In rats the most pronounced neuropathological findings have been dystrophic changes of terminal axons within the sensory nuclei of the spinal cord and medulla, especially the gracile and cuneate nuclei (1). In primates, long standing vitamin E deficiency, causes most severe axonopathy in the posterior column but peripheral nerves and the spinocerebellar tracts are also involved (19).

Clinical manifestations of vitamin E deficiency in humans are less well defined. There is substantial evidence that lack of vitamin E can cause a syndrome of hemolytic anemia, thrombocytosis and peripheral edema in premature infants, especially when a diet high in polyunsaturated fatty acids is supplemented with oxidant iron (20, 21). After infancy, vitamin E appears to contribute only marginally in vivo to the stabilization of erythrocyte membranes (22), for older children with vitamin E deficiency secondary to β-lipoproteinemia (23) or cystic fibrosis (24) have

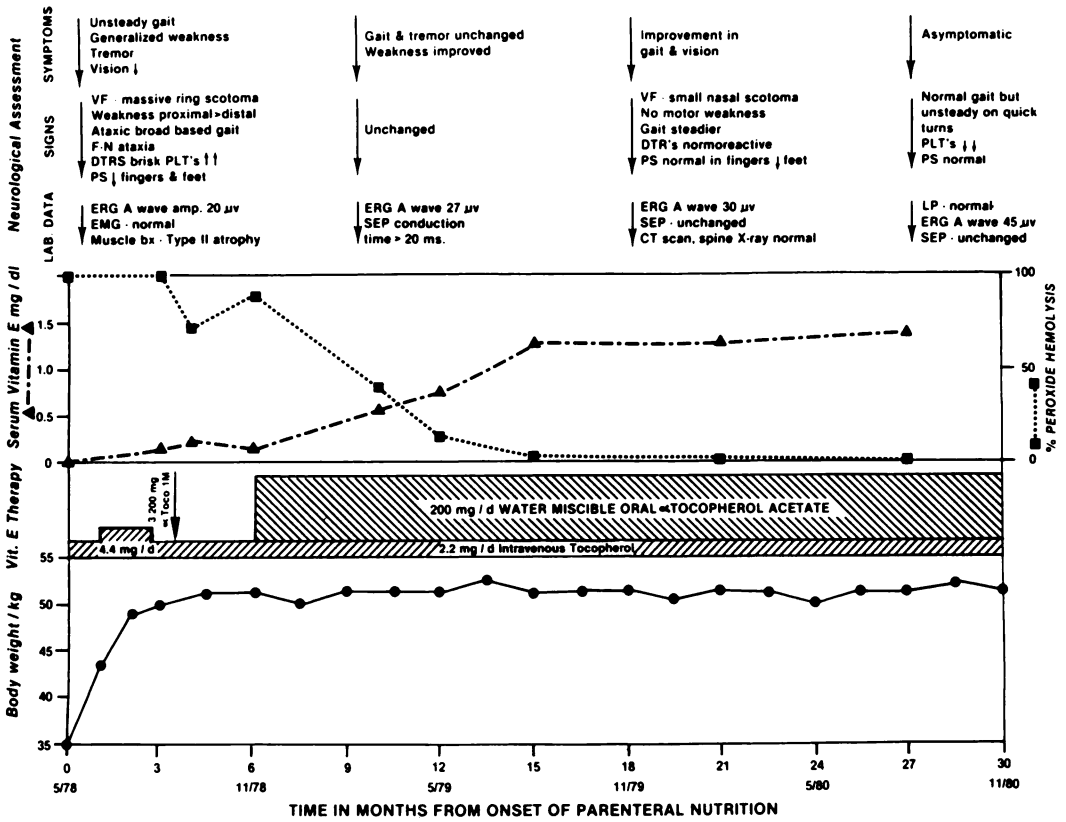

FIG. 2. The time sequence between the patient's neurological improvement and his vitamin E depletion. Abbreviations: VF, visual fields; FN, finger to nose, DTR, deep tendon reflexes; PLTs, plantar responses; PS, position sense; muscle bx, muscle biopsy; SEP, sensory evoked potential; ERG, electroretinogram; EMG, electromyogram.

shown shortening of erythrocyte survival but no clinical manifestations of overt hemolytic anemia. The anemia in our patient was probably due to several factors including protein calorie malnutrition (25) and iron deficiency from his underlying inflammatory bowel disease. The laboratory studies did not suggest hemolysis as a major cause of his anemia, although a shortened red cell life span may have been a contributing defect.

Several lines of evidence point to a probable relationship between lack of vitamin E and disease of the CNS in humans. Autopsy studies on children with cystic fibrosis (2, 3) and biliary atresia (5) have described neuroaxonal degeneration of the gracilis fasciculus. In β-lipoproteinemia, the clinical syndrome of ataxia, retinal degeneration and hemolysis (5, 26–28) has been linked to vitamin E deficiency, and there are some preliminary reports that early vitamin E therapy can prevent the neurological abnormalities from developing (6). Two recent reports describe a syndrome of very low vitamin E levels associated with ataxia, hyporeflexia, and restriction of upward gaze in six children with chronic liver disease (4) and in four adults with chronic fat malabsorption since childhood (7). Two of the adults had extensor plantars, and these same patients had some clinical improvement on long-term vitamin E therapy. Details of retinal function in these patients were not given. Finally, a rare familial disorder has been described in which "sea blue" histiocytes have been associated with posterior column dysfunction, brisk tendon reflexes, bilateral Babinski signs and very low serum vitamin E levels (8). In all these situations the vitamin E deficiency was probably present from early infancy where there is obviously a greater potential for affecting the developing nervous system. The findings in our patient, however, suggest that prolonged and very severe vitamin E deficiency may

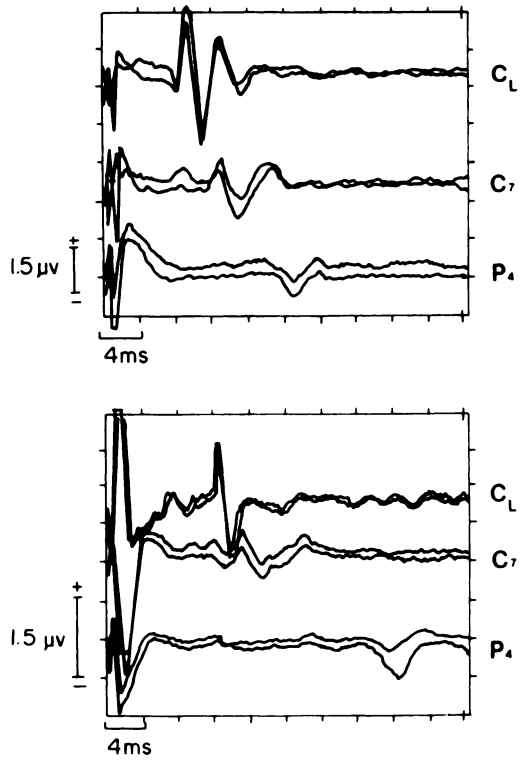

FIG. 3. Somatosensory evoked potentials of the patient (*bottom*) compared to those of a normal adult (*top*). The median nerve is stimulated at the wrist and the resulting potentials are recorded from midclavicle (C_L), seventh cervical vertebral process (C_7), and contralateral parietal scalp (P_4). In the patient the latency between C_L and P_4 potentials is 20.14 ms (normal 10.71 to 12.11 ms). Stimulus artifact at the left end of record.

also pose a threat to the fully developed central nervous system. This patient has been subject to severe steatorrhea for many years, requiring parenteral supplements of vitamins A, D, K, and B_{12} for 8 of these years. Thus he obviously was a strong candidate for prolonged and severe vitamin E deficiency. He had a gradual onset of gait and visual difficulties, and objectively he had evidence of posterior column dysfunction, an ataxic gait, brisk reflexes, a bilateral Babinski response, retinal pigment degeneration and decreased visual fields. While this neurological syndrome in many respects is akin to that described in the early onset vitamin E-deficient cases (4, 7) our patient had clear-cut upper motor neurone findings while the children had hyporeflexia and more evidence of peripheral neuropathy. This may represent a difference in suspectibility of peripheral nerves to vitamin E deficiency in children compared with adults. The extensor plantar responses in the adults with early onset vitamin E deficiency (7) and the spinocerebellar degeneration of primates with long standing vitamin E deficiency (19) would suggest that several areas of the CNS may eventually become involved, even though the axonopathy of the posterior columns is the most striking feature. Obviously superimposed vitamin B_{12} deficiency should also be considered, however, this is highly unlikely in our patient since he had received monthly parenteral B_{12} for many years, and his initial serum B_{12} levels measured microbiologically and by radioimmunoassay were entirely normal.

Undoubtedly his severe cachexia contributed to his initial weakness, however, his recovery from protein-calorie malnutrition was rather rapid, after the onset of parenteral nutrition, and yet his gait and visual disturbances persisted. Our group has reported earlier (39) on the prevalence of vitamin E deficiency in short bowel patients on home parenteral nutrition and the lack of an available reliable parenteral vitamin E supplement. Clearly the large dose of intramuscular vitamin E in an oil base was ineffective.

Fortunately this patient achieved gradual vitamin E repletion with pharmacological doses of water miscible *dl* α tocopherol acetate by mouth. As Figure 2 demonstrates, our patient's neurological recovery started 6 months after normalization of his vitamin E status and strongly suggests a metabolic connection between his neurological disturbances and deficiency of vitamin E.

The persistence of a delayed somatosensory conduction in the face of clinical improvement is not surprising since this is frequently described in demyelinating disorders and indeed provides a useful diagnostic purpose (30).

The question arises as to whether our patient's decreased linoleic acid levels contributed to his clinical syndrome. Since the membranes of the retinal rod outer segments contain an exceptionally high concentration of polyunsaturated fatty acids (31), they are probably dependent on an adequate supply of essential fatty acids and in an environment rich in oxygen, they are obviously particularly susceptible to lipid peroxidation.

Since our patient's low linoleic acid levels persisted throughout his clinical course this cannot explain his neurological improvement. There may be a component of essential fatty acid deficiency contributing to the residual retinal defects, however, neither retinitis pigmentosa nor electroretinographic abnormalities have yet been described in essential fatty acid deficiency. The significance of the low linoleic acid levels in long-term parenteral nutrition patients may reflect altered metabolic pathways rather than essential fatty acid deficiency since depressed levels are seen in patients receiving as much as 15 to 20% of their calories from linoleic acid (32). Recent animal studies (33, 34) indicate that in vitamin E deficiency there may be simultaneous breakdown of the rods and the accumulation of lipofuscin granules in the pigment epithelium. Furthermore vitamin E appears to have a role in preventing oxidative destruction of vitamin A stores which would lead to further damage in photoreceptor cells. It should be noted that the ERG abnormalities found in our patient could not be explained by simple vitamin A deficiency, in that scotopic (rods) and photopic (cones) functions were equally affected and there was marked loss of postphotoreceptor retinal function, whereas hypovitaminosis A affects photoreceptors only. The fact that he showed an increase in his electroretinographic A wave amplitude with vitamin E supplementation, suggests an improvement in function of his photoreceptor layer. The lack of change in his B wave amplitude indicates damage of Mueller cells of his retina, which are thought to structurally and functionally support the retinal neurons. These electroretinographic changes are intriguingly similar to those described by Toskes et al (35) in patients with long standing chronic pancreatitis. His patients had apparently normal vitamin A and zinc status, however, vitamin E status was unfortunately not evaluated.

Vitamin E has often been described as the "vitamin in search of a disease." This case history strengthens a likely connection between vitamin E and neurological function, and suggests that this can occur de novo in the adult nervous system and thus along with other fat soluble vitamins, vitamin E supplementation is important for patients with chronic steatorrhea.

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