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VITAMIN E DEFICIENCY AND NEUROLOGIC DISEASE[1]

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INTRODUCTION

Recent developments in the field of clinical nutrition have confirmed that vitamin E, long considered "a vitamin looking for a disease" (49), plays an essential role in maintaining the structure and function of the human nervous

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system. This recognition evolved slowly despite the well-known detrimental effect of vitamin E deficiency on the neuromuscular system of many experimental animal models (58). Vitamin E was discovered in 1922 by Evans & Bishop (20) as a factor that prevented fetal resorption in the laboratory rat. The neurologic role of vitamin E was first described in 1928 (21) when paralysis was observed in suckling offspring of vitamin-E-deficient mother rats. In the following decade "nutritional encephalomalacia" was described in the chick (62), and "nutritional muscular dystrophy" (25) was reported in guinea pigs and rats fed diets deficient in vitamin E. The similarities between human muscular dystrophy and nutritional muscular dystrophy in animals led to disappointing trials in the 1950s of high-dose vitamin E treatment that proved ineffective in altering the course of the human muscle diseases (6, 52).

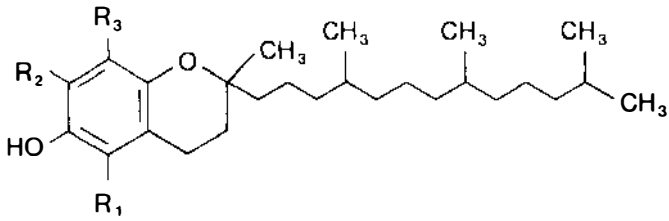
Because of similarities between the neurologic and ophthalmic findings of patients with a rare cause of severe steatorrhea and vitamin E deficiency, abetalipoproteinemia, and the neuromuscular abnormalities observed in experimental vitamin E deficiency in animals, Kayden et al (39) proposed in 1965 that vitamin E deficiency may be the cause of the neurologic dysfunction in these patients. Recent studies have clearly shown that vitamin E deficiency is responsible for the neurologic abnormalities that had been described in patients with various types of fat malabsorption disorders for decades (8). Recently, an inherited defect in vitamin E metabolism causing isolated vitamin E deficiency and neurologic degeneration in the absence of fat malabsorption has been recognized (40). In this review, pertinent aspects of vitamin E biochemistry and physiology, experimental models of vitamin E deficiency, and human vitamin E deficiency states are examined in the context of the neurological role of vitamin E in humans.

BIOCHEMISTRY OF VITAMIN E

The term "vitamin E" applies to a family of structurally related compounds, the tocopherols, which consist of hydroxylated chromanol rings linked to an isoprenoid side chain. The major forms of vitamin E (alpha, beta, delta, and gamma) differ by the number and position of methyl group substitution on the chromanol ring (Figure 1). Biologic activity differs substantially among forms; the ranking of vitamin E activity is alpha > beta > gamma, delta (37). All forms of vitamin E can be esterified at the phenolic group on the chromanol ring, although esters are uncommon in nature. Eight stereoisomers of vitamin E can be synthesized based on the rotational direction of the three methyl groups at the 2, 4', and 8' positions; however, only the R-R-R isomer (*d*-α-tocopherol) occurs substantially in nature. The synthetic form of vitamin E, *dl*-α-tocopherol, is more properly termed all-racemic α-tocopherol because it is actually an equal mixture of the eight possible isomers.

Vitamin E is strongly lipophilic and is, therefore, located almost exclusively in cellular membranes and the circulating lipoproteins. In the brain, vitamin E is localized primarily in the mitochondrial, microsomal, and synaptosomal subcellular fractions (91). Diplock & Lucy (18) proposed that the phytyl side chain of the vitamin E molecule interacts with polyunsaturated fatty acids present in membrane phospholipids, anchoring the vitamin E in an ideal position for free radical scavenging by the hydroxyl group on the chromanol ring.

The most widely accepted physiological function of vitamin E is its role as a scavenger of free radicals, preventing oxidant injury to cell membrane polyunsaturated fatty acids and thiol-rich proteins and thus preserving the structure and functional integrity of subcellular organelles (83). Supporting this mechanism for the protective role of vitamin E in the nervous system is the aggravating effect of diets high in polyunsaturated fatty acids, the substrate for lipid peroxidation (17), and the successful substitution of other antioxidants for vitamin E in reducing the neurologic manifestations of vitamin E deficiency in animal models (59, 69). A primary structural role for vitamin E in the control of cell membrane permeability and stability, originally proposed by Lucy (47), is supported by studies in model membranes (92) but has not been examined in cellular membranes. In animals, vitamin E deficiency may interfere with mitochondrial energy production in muscle (32) and with function of ubiquinone in the cytochrome chain in adrenocortical cells (34). Peroxidation of mitochondrial lipid constituents may be responsible for these effects. In addition, vitamin E has been postulated as a regulator



COMPOUND	R_1	R_2	R_3
α-tocopherol	CH_3	CH_3	CH_3
β-tocopherol	CH_3	H	CH_3
γ-tocopherol	H	CH_3	CH_3
δ-tocopherol	H	H	CH_3

Figure 1 Chemical structure of alpha-, beta-, gamma-, and delta-tocopherol.

of nucleic acid synthesis and gene expression (15). Finally, vitamin E may participate in controlling the synthesis of brain prostaglandins (51). Although it is not certain which mechanism is responsible for the functional and structural alterations of the nervous system and muscle during vitamin E deficiency, the role of vitamin E as an antioxidant accounts best for its protective effect.

PHYSIOLOGY OF VITAMIN E

Since symptomatic vitamin E deficiency in humans rarely occurs consequent to a pure dietary insufficiency but rather is caused by malabsorption of ingested vitamin E, an understanding of normal vitamin E absorption and transport is essential before describing the clinical circumstances underlying the vitamin E deficiency state. Approximately 20–40% of dietary vitamin E is normally absorbed by the intestine (10). Because of its hydrophobic nature, vitamin E requires micellar solubilization by bile acids secreted from the liver in order for the vitamin E to traverse the aqueous environment in the intestinal lumen and reach the surface of the absorptive enterocyte (23). Prior to intestinal absorption, most esters of vitamin E must be hydrolyzed by esterases secreted by the pancreas or found in the intestinal mucosa (57). Vitamin E is absorbed into the intestinal mucosa by a nonsaturable, passive diffusion process that is not carrier mediated (33). Once inside the enterocyte, vitamin E is incorporated with the other products of dietary lipid digestion and apolipoproteins into chylomicrons, which are transported into the mesenteric lymphatics and finally to the systemic circulation (Figure 2).

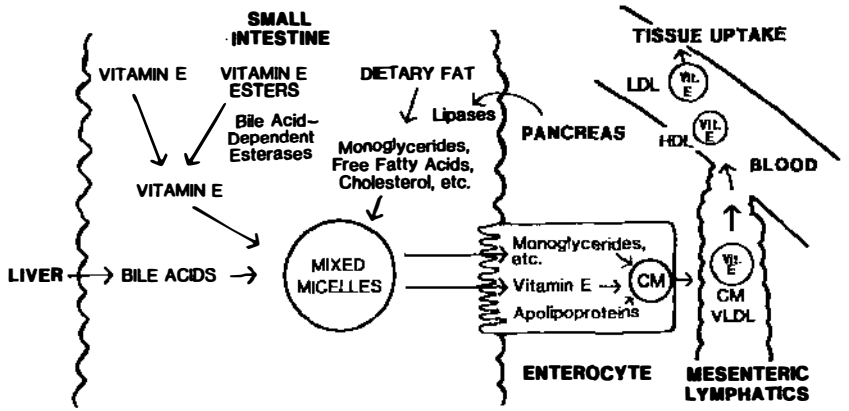


Figure 2 Schema of absorption and transport of vitamin E in man. Reproduced with permission from *Clinical and Nutritional Aspects of Vitamin E*, Amsterdam: Elsevier, 1987, pp. 169–81.

Vitamin E is most likely transported to the liver in chylomicron remnants and then secreted in very low density lipoproteins (VLDL) and perhaps high density lipoproteins (HDL). Most circulating vitamin E is found in LDL and HDL in the fasting state. Vitamin E is transferred to tissues through lipoprotein lipase hydrolysis of chylomicrons (87), receptor binding of LDL (85), and probably other uncharacterized mechanisms. Vitamin E is primarily stored in liver, a rapid turnover depot, and adipose tissue, which may be slow to release vitamin E that is stored in the lipid droplet (48, 86). Vitamin E is metabolized through oxidation and formation of quinones and other substances. Up to 8% of orally fed vitamin E may appear in the bile as metabolites, whereas less than 1% is eliminated in the urine. Thus, the majority of excreted vitamin E appears in the stool either as nonabsorbed dietary vitamin E or as biliary metabolites (24).

The precise mechanism by which vitamin E is transported from circulating lipoproteins to the brain and spinal cord and the factors regulating this transport have not been elucidated. However, there is a nonuniform distribution of vitamin E in the central and peripheral nervous systems (90). The medulla, spinal cord, and cerebellum, three sites affected during vitamin E deficiency, have significantly lower vitamin E content in young animals compared to other regions of the brain and compared with older animals. Interestingly, cerebellum has one of the highest rates of uptake of intravenously injected radiolabeled alpha-tocopherol compared to other nervous system tissues, which suggests that the cerebellum is particularly active in the metabolism or utilization of vitamin E (89). Thus, the susceptibility of certain brain regions to injury during vitamin E deficiency may relate to lower basal levels or higher utilization rates of vitamin E. In contrast, peripheral nerve, which also degenerates during vitamin E deficiency, actually contains more vitamin E than does brain (89).

VITAMIN E DEFICIENCY STATES

Animal Models

Dietary vitamin E deficiency in a variety of experimental animals leads to degeneration of the nervous system and skeletal muscle. These disorders provide useful animal models for the study of the pathogenesis and treatment of the human counterparts. When maintained on vitamin-E-deficient diets, growing chicks develop encephalomalacia and ataxia, rats and Rhesus monkeys develop neuroaxonal degeneration in the spinal cord and peripheral nerves and retinal abnormalities (31, 65), and many animal species show evidence of skeletal and cardiac myopathy (58). The striking similarities between histological lesions in man and those demonstrated in these animal models provided part of the basis for establishing a causal relationship between vitamin E deficiency and the human neurologic disorder.

Human Vitamin E Deficiency States

FAT MALABSORPTION DISORDERS Because of the close association between intestinal absorption of dietary fat and vitamin E, any perturbation of the processes essential to fat digestion and absorption will impair vitamin E absorption. Thus, low serum vitamin E concentrations have been observed in patients with a variety of fat malabsorption conditions (54). In the 1960s, Sung described a neuroaxonal dystrophy in the brainstem and spinal cord of children dying of cystic fibrosis (80) and extrahepatic biliary atresia (82), yet no impediments of neurological function had been appreciated in these vitamin-E-deficient children. It was not until the last decade that careful clinical study of children and adults with several specific causes of vitamin E malabsorption has conclusively demonstrated the existence of a neuromuscular disorder due to vitamin E deficiency in humans.

Abetalipoproteinemia is a rare inborn error of lipoprotein metabolism caused by an absence of apolipoprotein B, a component necessary for the secretion of chylomicrons. Thus, steatorrhea is present from birth because of the patient's inability to transport fat from the enterocyte to the mesenteric lymphatics. A progressive neuropathy and retinopathy develops in the first two decades of life, leading to crippling ataxia and impaired vision early in adulthood. Serum vitamin E levels are almost undetectable in patients with abetalipoproteinemia because of the absence of plasma β-lipoproteins. Clinical trials of high-dose vitamin E, initiated because of the similarities of the neurologic abnormalities to the experimental animal models of vitamin E deficiency, improved and prevented symptoms in young patients and arrested progression of neurologic and retinal dysfunction in older patients (5, 56).

In 1981, a degenerative neurologic disorder was characterized and linked to vitamin E deficiency in children with chronic cholestatic hepatobiliary disorders (66), including diseases such as extrahepatic biliary atresia, neonatal hepatitis, arteriohepatic dysplasia, and familial cholestatic syndromes. Cholestasis leads to insufficient intraluminal concentrations of bile acids, which in turn causes a failure of micellar solubilization and absorption of dietary fat (77). Profound malabsorption of vitamin E in children with severe cholestasis leads to biochemical evidence of vitamin E deficiency, elevated erythrocyte hemolysis in hydrogen peroxide (a functional measure of vitamin E deficiency), and depleted tissue stores (73, 77). Vitamin E deficiency is very common in children with chronic cholestasis, occurring in 50 to 77% of such children surveyed (1, 11, 74, 84), but less common in adults with acquired cholestatic disorders, such as primary biliary cirrhosis (70). The presence of vitamin E deficiency during childhood cholestasis correlates with neurologic symptomatology (Figure 3) (3, 27, 66, 74), the neuromuscular lesions (66) are similar to those in animal models of vitamin E deficiency and

in abetalipoproteinemia, and vitamin E repletional therapy is effective in preventing, arresting, or reversing the neurologic symptoms (2, 27, 64, 75). Neurologic findings are rarer in vitamin-E-deficient adults with chronic cholestasis, most likely because of remaining tissue stores and the apparent increased susceptibility of the developing nervous system to injury caused by vitamin E deficiency. The overall experience in children with cholestasis and vitamin E deficiency is similar to that reported in abetalipoproteinemia. Interestingly, the onset and progression of the neurologic syndrome is earlier and more rapid during chronic childhood cholestasis despite malabsorption from infancy in both disorders, which suggests the presence of an additional pro-oxidant factor in cholestasis.

Cystic fibrosis (CF), the most common lethal autosomal recessive disease in Caucasians, causes progressive destruction and fibrosis of the exocrine pancreas in most patients. This results in insufficient secretion of pancreatic enzymes that are essential for the digestion of dietary fat. Thus, steatorrhea and malabsorption of vitamin E are common consequences of cystic fibrosis, even when pancreatic enzyme supplements are orally administered to patients (22). Despite the common observations of low serum vitamin E levels in unsupplemented cystic fibrosis patients (22) and neuroaxonal lesions in the posterior columns of the spinal cord at autopsy (16, 80), overt neurological

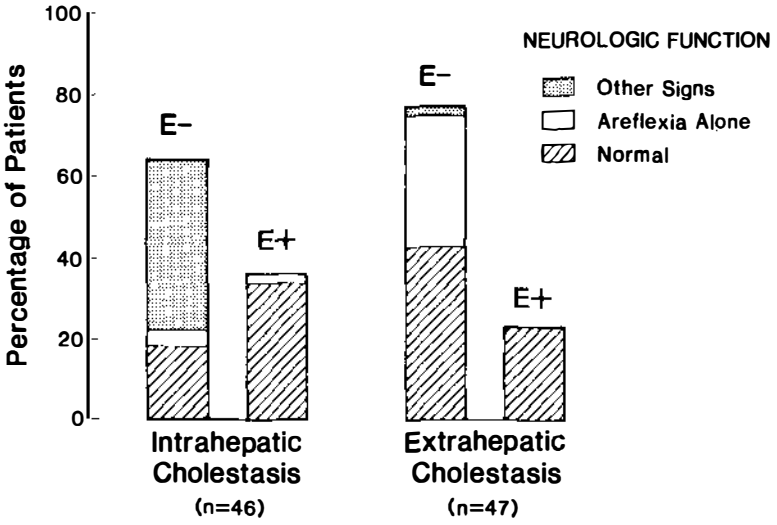


Figure 3 Presence of neurologic symptoms in children with intrahepatic cholestasis and extrahepatic cholestasis who are vitamin E deficient (E−) or vitamin E sufficient (E+). Reproduced with permission from *Clinical and Nutritional Aspects of Vitamin E,* Amsterdam: Elsevier, 1987, pp. 169–81.

disease is rare in vitamin-E-deficient CF patients. Of note is the observation that each reported case with neurological dysfunction also had very significant liver involvement caused by cystic fibrosis (14, 19, 95). It is not certain if the presence of liver disease in CF renders the vitamin E deficiency more severe, results in malabsorption of another contributing nutrient, or imposes an oxidant stress that hastens the development of neurologic dysfunction. As in abetalipoproteinemia and chronic childhood cholestasis, correction of the vitamin E deficiency state during cystic fibrosis stabilizes or reverses many of the neurologic symptoms (14, 19). There is also evidence from autopsy data that vitamin E supplementation reduces the severity of the neuroaxonal lesions in the spinal cord (81).

A similar vitamin-E-responsive neurologic disorder occurs in adults with prolonged steatorrhea after lengthy surgical resections of the intestine for treatment of Crohn's disease (30, 68), intestinal pseudoobstruction (30), or mesenteric vascular thrombosis (68), and with radiation enteritis (93). A loss of intestinal absorptive surface area and ileal malabsorption leading to fecal bile acid loss are responsbile for the impaired intestinal absorption of vitamin E in these conditions. In general, 10 to 20 years of severe fat malabsorption are required before symptomatic vitamin E deficiency develops in these acquired intestinal diseases. A pigmented retinopathy with visual disturbances and electrophysiologic abnormalities may accompany the neurologic symptoms.

ISOLATED VITAMIN E DEFICIENCY A unique inborn error in vitamin E metabolism has recently been discovered that causes an isolated deficiency of vitamin E in the absence of fat malabsorption or any evidence of gastrointestinal, liver, or lipoprotein abnormalities (13, 29, 40, 42, 44, 79, 96). In this disorder, neurologic symptoms generally appear within the first decade of life, although an adult-onset case has been described (96). Vitamin E deficiency has been unequivocally demonstrated in these patients by low serum vitamin E levels, low ratios of serum vitamin E to total serum lipid concentration (35), elevated hydrogen peroxide hemolysis, and low adipose tissue and sural nerve vitamin E content (88). Other causes of similar neurologic diseases have been excluded.

The cause of the vitamin E deficiency is unclear; however, it appears to be inherited in an autosomal recessive manner. Harding et al (29) claim that a selective defect of intestinal absorption of vitamin E is present in these patients. However, our studies demonstrate normal intestinal absorption of pharmacologic doses of vitamin E in four affected patients (40, 79) with a more rapid decline in serum vitamin E compared to controls during the 72 hours after the vitamin E loading dose. Yokota et al (96) have confirmed this phenomenon in their patient. Therefore, we postulate a defect in hepatic metabolism of the vitamin E that reaches the liver in chylomicron remnants.

Patients with this condition have clinical findings of neurologic dysfunction similar to those with disorders of fat malabsorption, and they show histologic lesions in muscle and peripheral nerve biopsies consistent with vitamin E deficiency (13, 42, 44, 79, 96). Furthermore, they respond to oral vitamin E supplementation. The discovery of this disorder now makes it necessary to examine vitamin E status in all patients with peripheral neuropathy and movement disorders. Studies in progress investigating this fascinating group of patients will undoubtedly lead to a better understanding of the normal physiology of vitamin E absorption and transport in humans.

Clinical Features of the Neurologic Disorder

Prolonged vitamin E deficiency causes a spinocerebellar ataxia in patients with secondary vitamin E malabsorption and with the isolated vitamin E deficiency syndrome. The most common findings include loss of deep tendon reflexes, truncal and limb ataxia, markedly diminished perception of vibration and position, impairment of eye movements (ophthalmoplegia), muscle weakness, ptosis, and dysarthria. A pigmented retinopathy may also occur, which results in visual field cuts and deterioration of visual function (36, 56). Through detailed clinical studies, it is now evident that there are distinct but overlapping constellations of neurologic abnormalities that track with the underlying cause of the vitamin E deficiency (Table 1). For instance, in the isolated vitamin E deficiency syndrome, ophthalmoplegia and pigmented retinopathy are extremely unusual and deep tendon reflexes may be normal.

The course of the neurologic disease follows a characteristic pattern. The largest and best-studied group of patients are those with vitamin E deficiency

Table 1 Clinical features of vitamin E deficiency disorders[a]

	Abetalipoproteinemia	Chronic childhood cholestasis	Other fat malabsorption disorders	Isolated vitamin E deficiency
Hypo/areflexia	++	++	++	±
Cerebellar ataxia	++	++	++	++
Loss of position sense	++	++	+	±
Loss of vibratory sense	++	++	++	++
Loss of touch-pain	+	±	+	–
Ophthalmoplegia	+	+	+	–
Ptosis	+	+	±	–
Muscle Weakness	+	+	+	+
Pigmented retinopathy	++	±	+	–
Dysarthria	+	±	+	±

[a]++ = always present, + = commonly present, ± = inconsistently present, – = absent.

associated with chronic childhood cholestasis. The clinical progression of the neurologic disorder is illustrated in Figure 4 by showing the percentage of vitamin-E-deficient children exhibiting each of five neurologic signs at two-year intervals. Hyporeflexia appears first at age 18–24 months; by age three to four years, a majority of children show definite evidence of neurologic dysfunction, and by age ten years, most have a disabling combination of neurologic deficits (74). Similar quantitation of the course of the neurologic manifestations of vitamin E deficiency associated with other disorders of fat malabsorption has not been reported. However, the progression of neurologic symptoms is slower (over 10 to 20 years) in adults with acquired short bowel syndrome and intermediate in patients with abetalipoproteinemia.

Recently, it has been proposed that vitamin E deficiency may be responsible for the varied psychomotor abnormalities seen in adults with chronic liver disease. Satel & Riely (67) suggest that vitamin E deficiency may contribute to the high incidence of behavioral and personality disorders observed in their patients with chronic cholestatic liver disease. In a preliminary report, Arria et al (4) demonstrated a correlation between psychomotor impairment on a battery of neuropsychologic tests and the presence of vitamin E deficiency in adults with advanced primary biliary cirrhosis being evaluated for possible liver transplantation. Additional clinical studies will be needed in order to

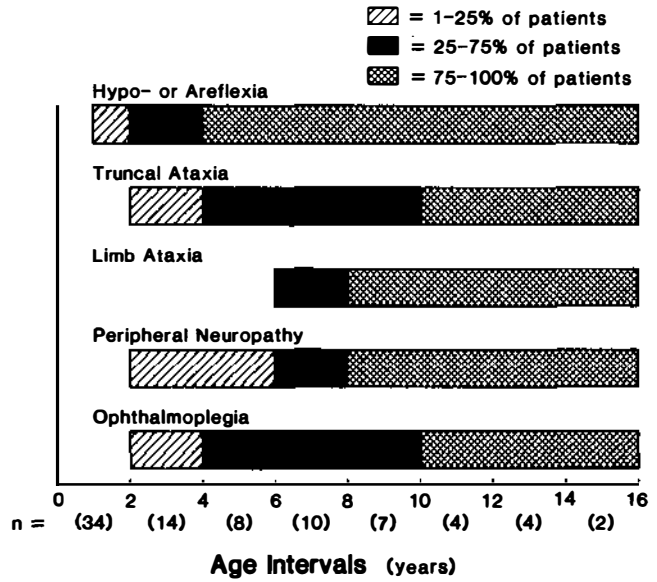


Figure 4 Percentage of vitamin-E-deficient children with chronic cholestasis who show evidence of neurologic abnormalities at two-year intervals. Reproduced with permission from *Am. J. Dis. Child.*, 1985; 139:1211–15.

confirm this postulated role of vitamin E in cognitive and behavioral processes.

Histopathology and Electrophysiology of Vitamin E Deficiency in Humans

Excellent correlation has been found between the clinical manifestations of vitamin E deficiency in humans and the histological lesions observed in biopsy or autopsy tissues. Swollen, dystrophic axons (spheroids) have been observed in the gracile and cuneate nuclei, posterior columns of the spinal cord, and Clarke's column; and degeneration of the posterior columns and dorsal and ventral spinocerebellar tracts was present at autopsy of two children with vitamin E deficiency secondary to chronic cholestasis (66). Cerebellar hemispheres showed mild atrophy, and loss of nerve-cell bodies was evident in the nuclei of the third and fourth cranial nerves. In addition, loss of predominantly large-caliber, myelinated axons in peripheral sensory nerve (Figure 5) has been an almost universal finding in patients with advanced vitamin E deficiency caused by cholestasis (43, 66, 77), abetalipoproteinemia (94), radiation enteritis (93), or the isolated vitamin E deficiency syndrome (13). Degenerating axons (66, 71, 93) and lipopigment deposition in Schwann cell cyctoplasm (13, 43, 96) in the absence of inflammation, fibrosis, or primary demyelination are also characteristic of the peripheral nerve lesions. Disturbances in function of the posterior columns, sensory nerves, and spinocerebellar tracts caused by these lesions account for the loss of vibratory and position sensation and truncal and limb ataxia that are commonly observed. The axonal, posterior column, and gracile and cuneate nuclei lesions are similar to those described in the vitamin-E-deficient rat (63) and Rhesus monkey (60).

Muscle lesions of two types have been described in patients with vitamin E deficiency caused by chronic cholestasis (3, 27, 61, 79), abetalipoproteinemia (41), and the isolated vitamin E deficiency syndrome (13, 42, 79, 96). A neuropathic lesion consists of variation in muscle fiber size without evidence of necrosis or inflammation and fiber-type grouping on NADH or ATPase staining (Figure 6); this most likely represents a denervation-renervation process. A myopathic lesion represents more intrinsic muscle fiber injury. Small, grain-like basophilic deposits are scattered throughout many muscle fibers. On frozen sections, these inclusions are autofluorescent and stain positive for esterase and acid phosphatase (60). Electron microscopy reveals that these deposits consist of numerous densely osmiophilic membrane-bound cytosomes lying between myofibrils (Figure 6). It has been suggested that these structures are secondary lysosomes containing lipopigment, a by-product of peroxidized membrane fatty acids (60). Areas of Z-band streaming

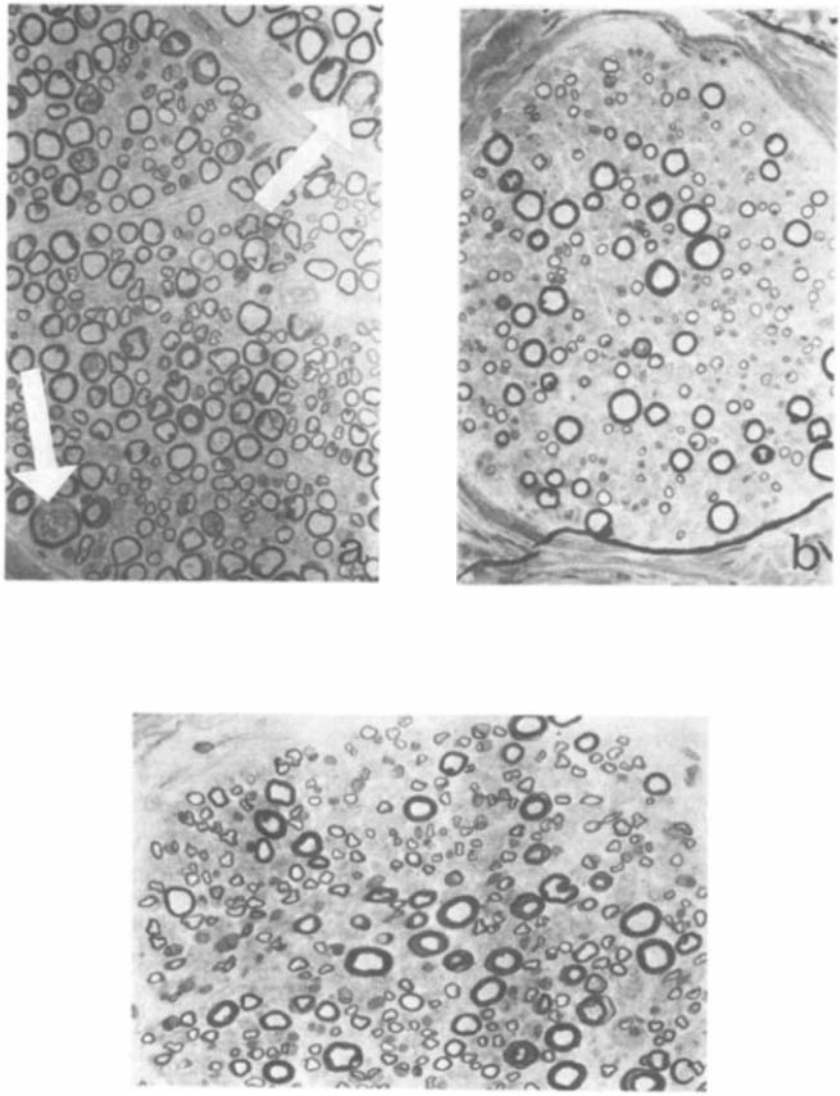


Figure 5 Peripheral nerve lesion in patients with vitamin E deficiency. *A*. Swollen, large-caliber myelinated axons with attenuation of myelin sheath *(arrowheads)* in an 11-month-old girl with chronic cholestasis. *B*. Decreased number of large-caliber myelinated axons in a 12-year-old girl with chronic cholestasis. *C*. Decreased number of large-caliber myelinated axons in a 14-year-old boy with abetalipoproteinemia.

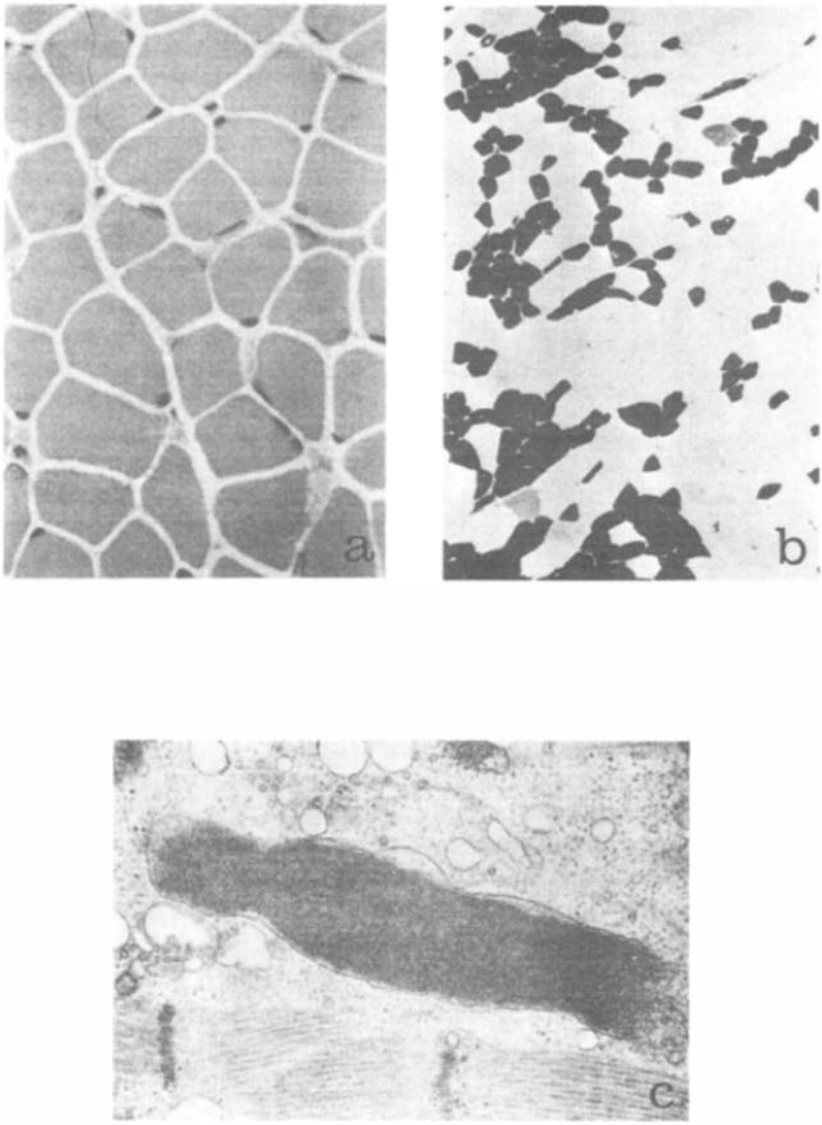


Figure 6 Muscle lesion in patients with vitamin E deficiency. *A*. Variation in size of muscle fibers. *B*. Fiber-type grouping evident on ATPase histochemical stain of muscle. *C*. Electron-dense, membrane-bound inclusion body lying between myofibrils on electron microscopy of muscle biopsy from a 12-year-old girl with vitamin E deficiency caused by chronic cholestasis.

and autophagocytic vacuoles containing debris are also seen. Similar lesions have been observed in skeletal muscle of vitamin-E-deficient rats (46).

Electrophysiologic studies indicate functional impairment of peripheral nerves, posterior columns, and the retina in patients with vitamin E deficiency, unrelated to the underlying cause. The most consistent finding in peripheral nerve conduction studies is diminished amplitudes of sensory nerve action potentials with variable delays in conduction velocities (3, 12, 27, 30, 68, 75, 79, 94), which indicates an axonopathy rather than a primary demyelinating process. Electromyography in older patients has revealed signs of denervation of muscles, presumably indicative of involvement of motor nerves. Somatosensory evoked response (SER) testing quantitates the speed of conduction of a peripheral sensory stimulus through peripheral nerves, spinal cord, and brainstem pathways to the cerebral cortex. Such tests demonstrate a central delay in conduction (12, 30, 36, 42, 68, 93, 96), correlating with the posterior column degeneration demonstrated histologically.

Functional abnormalities can be detected electrophysiologically in retina and optic nerve before changes are evident on ophthalmic examination. Visual evoked response testing and electroretinography have revealed abnormalities in retinal function in vitamin-E-deficient patients with chronic cholestasis (3, 45), cystic fibrosis (50), short bowel syndrome (30, 36), and isolated vitamin E deficiency syndrome (42). The synergistic role of concomitant vitamin A deficiency in leading to these electrophysiologic abnormalities has not been completely determined; however, rats and monkeys have more extensive retinal degeneration when both vitamins A and E are deficient compared to either vitamin alone (31, 65). Human electrophysiologic abnormalities have improved following therapy with vitamin E alone.

PATHOGENESIS OF NEUROLOGIC DYSFUNCTION

The pathophysiologic mechanisms underlying the vitamin E deficiency neuromuscular syndrome are not known, but are most likely related to insufficient antioxidant protection in neural and muscle tissues against free radical oxidant injury to membrane unsaturated fatty acids. A growing body of evidence favors this association. When animals are placed on vitamin-E-deficient diets and following the onset of fat or vitamin E malabsorption in man, a latency period of variable duration is observed during which endogenous vitamin E stores are depleted but neurological function is maintained. In rats, the content of vitamin E in liver and adipose tissue decreases by 95% after eight weeks of vitamin E deprivation, whereas brain and spinal cord content are preserved to a much grater extent (53). The latency period before the onset of

neurologic dysfunction is only 18–24 months in infants with cholestatic liver disease (74), which reflects diminished vitamin E stores at birth compounded by severe malabsorption of dietary vitamin E (77). In contrast, 10 to 20 years of steatorrhea and vitamin E malabsorption precede the onset of neurologic disease in adults who presumably had normal stores of vitamin E prior to developing steatorrhea. The latency period may be several years to over a decade in children with abetalipoproteinemia who also malabsorb vitamin E from birth. Since children with either chronic cholestasis or abetalipoproteinemia develop profound vitamin E deficiency during infancy, the more rapid course of the neurologic disease during childhood cholestasis suggests that additional pro-oxidant stresses may develop as a result of perturbed hepatic function.

The increased susceptibility of certain anatomic regions of the nervous system may be related to local differences in concentration of tocopherol, peroxidizable unsaturated fatty acids, and other pro- and antioxidant compounds. Vatassery et al (89–91) have shown that the concentrations of vitamin E in the spinal cord and cerebellum in the rat and guinea pig are lower than at other sites of the central nervous system. Local differences in the production and sequestration of free radicals produced by normal oxidative processes may also predispose certain areas of the brain to injury. Although there is no compensatory increase of the endogenous antioxidants (glutathione peroxidase and superoxide dismutase) in the nervous system of vitamin-E-deficient rats (53), treatment with other exogenous compounds with antioxidant activity appeared to ameliorate the histologic injury in the cuneate nucleus of vitamin-E-deficient rats (59).

Additional evidence supporting the association between antioxidant activity of vitamin E and its neurologic role can be found in studies of tissue histology. The accumulation of breakdown products of membrane lipids (lipopigment) in Schwann cell cytoplasm, dorsal root ganglia, and skeletal muscle has been demonstrated repeatedly in humans with the vitamin E deficiency neurologic disorder. In addition, one of the earliest findings in the sural nerve lesion of vitamin-E-deficient children is tortuosity and invagination of the axonal membrane of large-caliber myelinated axons (71); this supports the view that membrane instability or damage is an early event in this type of nerve injury. Finally, low tocopherol levels in peripheral nerve may precede the onset of histological lesions in vitamin-E-deficient patients with peripheral neuropathy (88), which suggests that biochemical or compositional changes in nerve accompanying vitamin E deficiency are sufficient to impair the function of the nerve. Although these data do not prove a causal relationship between the antioxidant activity of vitamin E and its neurologic role, there are no inconsistencies to this hypothesis based on available information.

TREATMENT OF VITAMIN E DEFICIENCY

Chronic Childhood Cholestasis

The final bit of evidence truly linking vitamin E deficiency to the characteristic neurologic disorder already described has been the demonstration that correction of the vitamin E deficiency state, without other therapeutic manipulations, leads to reversal and prevention of the neurologic symptoms. The largest group studied has been those children with vitamin E deficiency caused by chronic cholestasis. Because of the extremely impaired intestinal absorption of vitamin E in children with severe cholestasis (73, 77), correction of the vitamin E deficiency requires either very high doses of standard oral preparations of vitamin E (up to 100–200 IU/kg/day) or the administration of parenteral vitamin E by intramuscular injection. Guggenheim et al (27) first reported improved neurologic function in four children with chronic cholestasis after six to fourteen months of vitamin E repletion. This report was followed by four larger studies (2, 64, 72, 75), summarized in Table 2. Of 39 children with well-documented vitamin E deficiency who underwent repletional therapy for one to four years, neurologic symptoms were prevented in 29%, stabilized in 28%, and improved in 46% of the patients. No patient had progression of dysfunction during vitamin E therapy. Symptoms did not respond uniformly or at the same rate; the older, more severely affected patients had more limited restitution of neurologic function (2, 75). For these reasons, evaluation for and correction of vitamin E deficiency is now recommended in the first year of life in children with cholestatic hepatobiliary disorders.

Vitamin E status can be evaluated by measuring serum vitamin E concentrations by either fluorometric (28) or high pressure liquid chromatography (7) techniques, by examining red blood cell hemolysis in hydrogen peroxide, by measuring pentane in the expired air (17a), by measuring vitamin E tissue stores (38, 88), or by calculating the ratio of serum vitamin E to total serum lipid concentrations (mg/g) (35). Because serum lipid levels are elevated during cholestasis, serum vitamin E levels alone do not accurately reflect vitamin E status, presumably because vitamin E can partition into the intravascular lipid compartment from cellular membranes. Indeed, cholestatic children with marked hyperlipidemia may be vitamin E deficient yet have apparently normal serum vitamin E levels (78). Therefore, the ratio of serum vitamin E to total lipids is monitored in order to correct for hyperlipidemia (35). Vitamin E deficiency is defined as a ratio < 0.8 mg/g for children age 12 years or older and < 0.6 mg/g for younger children.

Once vitamin E deficiency is identified, treatment should be started with large oral doses of available preparations of vitamin E, starting with 50

Table 2 Effect of vitamin E treatment on neurological symptoms in 39 children with chronic cholestasis

Trial	Prevented	Stabilized	Improved	Progressed
Alvarez, 1985 (2)	6	4	7	0
Sokol, 1985 (75)	2	1	11	0
Perlmutter, 1987 (64)	0	6	0	0
Sokol, 1987 (72)	2	0	10	0
Total	10 (26%)	11 (28%)	18 (46%)	0 (0%)

IU/kg/day and advancing by 50-IU/kg/day increments up to 150–200 IU/kg/day, given as a single morning dose with breakfast several hours before any other medications (e.g. cholestyramine) that interfere with vitamin E absorption. Changes in vitamin E dose are dictated by monitoring the ratio of serum vitamin E to total lipids.

If vitamin E status fails to normalize after several months of the maximal dose and the child is over 9–12 months of age, therapy is started with intramuscular injections of vitamin E to provide for an average of 1–2 mg/kg/day. The preparation used in the United States (Ephynal®; Hoffmann-LaRoche, Inc.) contains 50 mg of *dl*-alpha-tocopherol per ml, in 1.0-ml ampules. We administer one ampule intramuscularly per dose and calculate the dosing interval to provide the recommended dose. Preliminary studies now indicate that a water-soluble form of vitamin E, *d*-alpha-tocopheryl polyethylene glycol-1000 succinate (TPGS, Eastman Chemical Products, Inc., Kingsport, TN) at an oral dose of 15–25 IU/kg/day may be effective at normalizing vitamin E status and reversing neurologic dysfunction (72, 76), obviating the need for intramuscular injections. Unfortunately, neither Ephynal nor TPGS have yet been released for general use in the United States; however, Ephynal can be obtained from the manufacturer on a case-by-case basis. Our current experience is that vitamin E repletional therapy must be continued for at least several years in cholestatic patients before tissue stores are repleted.

Abetalipoproteinemia

Following the initial suggestion that vitamin E deficiency might be the cause of the neurologic and retinal degeneration in abetalipoproteinemia (39), several groups supplemented patients with large oral doses of vitamin E, usually in combination with vitamin A. Five to 15 years of follow-up of these patients show clearly that the neurologic symptoms and electrophysiologic abnormalities as well as retinal dysfunction can be stabilized in older patients

and completely avoided if therapy is begun early in life (5, 9, 56). Treatment with 100–200 mg/kg/day of oral vitamin E in two or three divided doses is now recommended. Supplementation with 15,000 to 20,000 IU/day of vitamin A may also be necessary for optimal treatment of the retinal degeneration (5, 9, 55). Because of the absence of circulating beta-lipoproteins that normally transport most of the plasma vitamin E, serum vitamin E measurements do not accurately reflect vitamin E status in abetalipoproteinemia. Therefore, therapy is best monitored by peroxide hemolysis testing (26) or analysis of vitamin E stores in adipose tissue biopsies (38). Serial electrophysiologic study of retinal and somatosensory pathways may also prove useful in determining the functional adequacy of vitamin E treatment.

Cystic Fibrosis and Other Fat Malabsorption Disorders

In patients with cystic fibrosis who receive oral supplementation with pancreatic enzyme preparations, 5 to 10 IU/kg/day of oral vitamin E is generally effective in normalizing serum vitamin E levels in the absence of serious liver involvement. Cystic fibrosis patients with cholestatic liver disease should be evaluated and treated in the same manner as other children with chronic cholestasis. In the absence of hyperlipidemia, serum vitamin E levels above 5 μg/ml indicate the adequacy of vitamin E treatment.

Adults with other steatorrheic conditions generally show clinical and electrophysiologic improvement after large oral doses of vitamin E (200–3600 mg per day) (30, 36, 68). If parenteral nutrition is being administered, the 15 IU per day of alpha-tocopheryl acetate that is usually given in the standard intravenous multiple vitamin supplement will adequately prevent or reverse vitamin E deficiency. Rarely are intramuscular injections of vitamin E necessary in this clinical circumstance. Since over ten years of vitamin E deficiency may be necessary before overt neurologic symptoms develop in these patients, asymptomatic vitamin E deficiency may be much more common in adults with chronic steatorrhea than previously appreciated. Consequently, periodic serum vitamin E levels and ratios of serum E to total lipids should be incorporated into the usual laboratory monitoring of patients with ongoing steatorrhea. If deficiency is suspected, neurologic evaluation should precede repletional therapy.

Isolated Vitamin E Deficiency

Although the specific defect in vitamin E metabolism responsible for the isolated vitamin E deficiency syndrome is unknown, therapy improves neurologic function. The five reported cases (13, 29, 42, 44, 96) and our own four cases (40, 79) have all responded to 800–3600 mg/d of oral *dl*-alpha-

tocopherol or tocopheryl acetate, with most patients requiring the lower dose. As in other causes of vitamin E deficiency, patients whose neurologic deterioration is more advanced before therapy is instituted show a more limited response. For this reason and because these patients have no gastrointestinal symptoms, all patients being evaluated for movement disorders or peripheral neuropathy should be screened for vitamin E deficiency by measuring serum vitamin E level and the ratio of serum vitamin E to total lipids. These patients are clinically indistinguishable from scores of patients with untreatable forms of idiopathic or familial ataxia and neuropathy. Only through routine screening for vitamin E deficiency will these patients be identified, and the true incidence of isolated vitamin E deficiency thus be determined.

SUMMARY

During the recent resurgence of interest in the clinical uses of vitamin E, one of the major foci of attention has been the neurologic role of vitamin E in humans. Studies in patients with secondary vitamin E deficiency, caused by fat malabsorption disorders and total parenteral nutrition lacking an adequate supply of vitamin E, have elucidated a clinical disorder and histologic lesions of the nervous system and muscle that closely resemble those of experimental vitamin-E-deficient animal models. Investigations of the primary form of human vitamin E deficiency, the isolated vitamin E deficiency syndrome, have further substantiated the relationship between neurologic dysfunction and human vitamin E deficiency. It is now clear that vitamin E is an essential nutrient necessary for the optimal development and maintenance of the integrity and function of the human nervous system and skeletal muscle. The task for future study is to determine the mechanism by which vitamin E deficiency causes degeneration of selective regions of the nervous system and to investigate possible benefits of vitamin E supplementation in other neurologic disorders. In addition, further study of the isolated vitamin E deficiency syndrome promises to teach us more about normal physiologic mechanisms of vitamin E absorption and transport in humans.

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