CLINICAL NOTE

Electrophysiologic Recovery After Vitamin E–Deficient Neuropathy

Hyun-Yoon Ko, MD, Insun Park-Ko, MD

ABSTRACT. Ko H-Y, Park-Ko I. Electrophysiologic recovery after vitamin E–deficient neuropathy. Arch Phys Med Rehabil 1999;80:964-7.

A case report is presented of an electrophysiologic recovery from vitamin E–deficient neuropathy after treatment with water-soluble vitamin E in a patient with chronic hepatobiliary disease. The patient was a 64-year-old man who had experienced progressive difficulty in ambulation, with ataxia, over the previous 3 years. The symptoms were associated with pain, tingling sensation in the extremities, and reduced fine motor activity. The patient had chronic hepatobiliary disease, with recurrent cholangitis and external drainage of bile acid through a T-tube for more than 20 years. Vitamin E level was barely detectable (<0.5mg/L). Sensory conduction was absent in both sural nerves. Other sensory and motor conduction studies in the upper and lower extremities showed decreased amplitude. The patient was treated with water-soluble vitamin E. After 4 months of therapy, his ambulation function improved, but pain and tingling sensation in both hands remained. Sensory nerve action potentials appeared in both sural nerves, and amplitudes of other sensory nerves were increased. In a second follow-up study after 9 months, all of the evaluated parameters in the nerve conduction studies, as well as the vitamin E level, were normal. The authors conclude that vitamin E–deficient neuropathy is reversible and electrophysiologic recovery can occur with water-soluble vitamin E therapy.

VITAMIN E ACTS in concert with several reactions to protect living cells from damaging oxidative effects.[1] Ingested vitamin E requires intestinal solubilization by bile acids into mixed micelles so that the highly hydrophobic vitamin E can transverse the aqueous environment in the intestinal lumen to reach the surface of the absorptive enterocyte, where 20% to 40% of vitamin E is absorbed.[2,3] Impairment of any of the processes of vitamin E solubilization, absorption, or transport leads to malabsorption and eventual deficiency of vitamin E.[2] During cholestatic liver disease, impaired secretion of bile acids by the liver may result in intraluminal bile acid concentrations below the critical micellar concentration, causing severe malabsorption of vitamin E.[3]

Vitamin E is essential for normal neurologic structure and function; however, there is virtually no information regarding its uptake by neural tissues.[4] The mode of action of vitamin E in the nervous system has not been established. It appears to be important in maintaining the integrity and stability of biological membranes.[5] Binder and colleagues[6] were the first to suggest a possible relationship between neurologic dysfunction and vitamin E deficiency in patients with steatorrhea. Neurologic dysfunction from vitamin E deficiency can be prevented by timely and adequate supplementation with vitamin E.[7]

Once vitamin E deficiency is detected, treatment should be started with large oral doses of available preparations of vitamin E. A water-soluble ester of vitamin E, *d*-α-tocopherol polyethylene glycol-1,000 succinate (TPGS), is absorbed after oral administration in patients with severe cholestasis.[8] TPGS does not depend on fat malabsorption for uptake into intestinal cells because TPGS forms a micellar solution at low concentrations and thereby obviates the requirement for bile acids for vitamin E absorption.[3,9]

Reports of vitamin E deficiency followed by electrophysiologic recovery have not been found in the literature. We present a patient with chronic hepatobiliary disease who experienced electrophysiologic recovery from vitamin E–deficient neuropathy after treatment with water-soluble vitamin E.

CASE REPORT

A 64-year-old man reported that he was beginning to experience lack of balance and difficulty writing by hand. This off-balance sensation had been slowly progressing, and he had been falling frequently as a result. Since January of 1995, he had felt hypersensitivity and pain in the fingers of both hands and, gradually, in both of his feet. His medical history was notable for chronic hepatobiliary disease, with recurrent cholangitis and external drainage of bile acid through a T-tube for more than 20 years. He had undergone multiple surgeries, including choledochojejunostomy with multiple corrections in 1975, 1980, and 1983. On motor examination, tone was normal in all four extremities, and reflexes were absent in all extremities. Sensory examination revealed intact light touch, pinprick, and temperature sense; however, proprioception was markedly impaired on the distal upper and lower extremities. On plantar responses, the toes were downgoing. He had grade 5 strength in the proximal and distal regions in all four extremities. He had a tendency to walk stiffly and carefully, but did not fall. His gait was wide-based and ataxic. He had a markedly positive Romberg sign. Cranial nerve functions were normal. He could perform all activities of daily living independently. He was, however, walking with the use of a cane in his right hand. Walking in the dark had become particularly difficult.

Magnetic resonance imaging of the brain showed a small lesion of T2 prolongation in the left pontomedullary junction. Nerve conduction studies demonstrated low amplitude in the peroneal and tibial motor compound muscle action potentials on the right; and sural nerve conduction was absent bilaterally. On electromyography, there were a few fibrillation potentials

From the Department of Rehabilitation Medicine, Pusan National University Hospital, Pusan National University College of Medicine (Dr. Ko), and the Department of Rehabilitation Medicine, Inje University Pusan Paik Hospital (Dr. Park-Ko), Pusan, Korea.

Submitted for publication September 16, 1998. Accepted in revised form December 18, 1998.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

Reprint requests to Hyun-Yoon Ko, MD, Department of Rehabilitation Medicine, Pusan National University Hospital, Pusan National University College of Medicine, 1-10 Ami-Dong, Suh-Ku, Pusan 602-739, Korea.

0003-9993/99/8008-5212$3.00/0

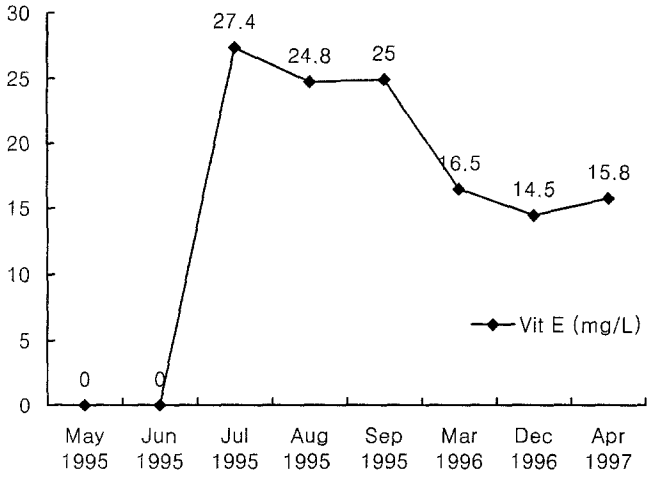

Fig 1. Time course of plasma α-tocopherol concentrations during supplementation with water-soluble vitamin E.

and positive sharp waves in the muscles sampled in the upper and lower extremities distally, with mild abnormality in motor unit recruitment. Biochemical findings included the following levels: α-tocopherol, <0.5mg/L (normal, 4.6 to 14.5mg/L); vitamin B12, 384pg/mL (normal, 211 to 960pg/mL); folate, 12.5ng/mL (normal, 2.7 to 21.0ng/mL); vitamin A, 48μg/dL (normal, 28 to 94 μg/dL); total bilirubin, 1.5mg/dL (normal, 0.2 to 1.4mg/dL); alanine aminotransterase, 64U/L (normal, 3 to 40U/L); and alkaline phosphatase, 230U/L (normal, 47 to 137U/L). Complete blood count, erythrocyte sedimentation rate, and levels of blood urea, blood glucose, and electrolytes were normal.

Because of the combination of undetectable plasma vitamin E concentrations, neurologic signs, and abnormal nerve conduction studies and electromyography, the patient was diagnosed to have a vitamin E–deficient polyneuropathy, presumably caused by fat malabsorption. He began treatment with water-soluble vitamin E (TPGS) (TwinLab Liqui-E[a]) at a dose of 550IU per day by mouth.

Vitamin E Status and Functional Change

Two weeks after the diagnosis in May 1995, the patient was given water-soluble vitamin E. During the next 37 days, his plasma α-tocopherol level increased to 27.4mg/L (normal, 4.6 to 14.5mg/L). After 4 months of therapy, the patient reported improvement of motor and sensory functions, although no objective improvement could be demonstrated except for slightly improved ataxia. During TPGS treatment the patient's neurologic abnormalities did not worsen. He continued to find walking in the dark difficult, however. His plasma vitamin E concentration was checked approximately every month; in August it was 24.8mg/L, and in September it was 25.0mg/L. The patient was reevaluated in April 1997. His plasma vitamin E level was 15.8mg/L. His symptoms and the findings on examination had stabilized. He reported that he was more steady on his feet and that his hand coordination had improved. His limbs were hypotonic with preservation of strength, and he was slightly ataxic when walking. Deep tendon reflexes were absent, and the plantar responses were flexor. He could walk, only occasionally requiring the assistance of a cane. His wide-based ataxic gait had improved, and Romberg test was equivocal. Biochemical levels were as follows: total bilirubin, 1.8mg/dL, and alkaline phosphatase, 235U/L. He continued supplementation of TPGS at a dose of 550IU per day. The time course of the patient's plasma α-tocopherol concentrations during supplementation with TPGS is presented in figure 1.

Nerve Conduction Study and Electromyography

The first electrophysiologic study was conducted in May 1995, 2 weeks before treatment with water-soluble vitamin E. The study demonstrated low amplitudes in the compound muscle action potentials of the right peroneal nerve (2.2mV) and tibial motor nerve (0.5mV) (table 1), and sural sensory responses were bilaterally absent. The distal latencies and conduction velocities of the tibial and deep peroneal nerve were within normal limits. Both S1 H-reflexes were absent. The amplitudes of the median and ulnar nerve sensory action potentials were decreased, 12μV and 14.8μV, respectively. On electromyography, there was only minimal fibrillation in both lower legs and feet and in the forearms and hands (table 2), with mixed or high mixed grade of motor unit action potential recruitment.

The second examination in November 1995 showed what appeared to be normal sural sensory potentials with vastly improved tibial and peroneal motor responses on the right side (table 1). Electromyography revealed possible improvement in the muscles that had been tested previously (table 2).

The third examination, performed in February 1996, showed

Table 1: Nerve Conduction Studies

		Distal Stimulation				Proximal Stimulation							
			Latency (msec)			Latency (msec)		Velocity (m/sec)			Amplitude		
Nerve	Recording	Distance (cm)	Exam 1	Exam 2	Normal	Exam 1	Exam 2	Exam 1	Exam 2	Normal	Exam 1	Exam 2	Normal
R Median-S*	2nd finger	14	2.8	3.2	≤3.4						12μV	16.3μV	≥16.6
R Ulnar-S*	5th finger	14	2.7	3.0	≤3.5						14.8μV	15.0μV	≥15.0
R Sural-S*	Lateral foot	14	NR	3.9	≤3.8						NR	8.9μV	≥7.5
L Sural-S*	Lateral foot	14	NR	3.8	≤3.8						NR	7.6μV	≥7.5
R Median-M	APB	8	4.7	4.7	≤4.0	9.8	10.1	50	50.8	≥52.9	9.3mV	9.5mV	≥8.2
R Ulnar-M	ADQ	8	3.9	4.1	≤3.7	7.2	7.9	51.1	53.9	≥56.8	11.8mV	10.4mV	≥4.2
R Tibial-M	AH	8	5.4	5.1	≤3.9	14.5	13.8	43.9	48.2	≥37.3	0.5mV	9.1mV	≥6.3
R Peroneal-M	EDB	8	4.8	5.9	≤5.3	11.8	11.4	44.2	46.1	≥44.6	2.2mV	4.5mV	≥3.2
R H-reflex	Soleus		NR	NR									
L H-reflex	Soleus		NR	NR									

Abbreviations: Exam 1, study performed May 1995; Exam 2, study performed November 1995; R, right; L, left; S, sensory; M, motor; APB, abductor pollicis brevis; ADQ, abductor digiti quinti; AH, abductor hallucis; EDB, extensor digitorum brevis; NR, no response.
* Sensory nerve conduction studies were performed by antidromic stimulation. The latency of sensory nerve action potential was measured to the negative peak of the response.

Table 2: Needle Electromyography

Muscle	Insertional Activity	At Rest				On Volition	
		PW		Fib		Recruitment	
		Exam 1	Exam 2	Exam 1	Exam 2	Exam 1	Exam 2
R EDB	Increased	+	+	+	+	M	HM
R AH	Increased	+	+	+	+	LM	M
R TA	Increased	+	+	+	+	HM	F
R APB	Increased	+	0	+	0	HM	F
R 1DIO	Increased	+	0	+	0	HM	F

Abbreviations: PW, positive sharp waves; Fib, fibrillation potentials; Exam 1, study performed May 1995; Exam 2, study performed November 1995; EDB, extensor digitorum brevis; AH, abductor hallucis; TA, tibialis anticus; APB, abductor pollicis brevis; 1DIO, first dorsal interosseus; 0, absent; +, a few; M, mixed degree of motor unit recruitment; LM, low mixed degree of motor unit recruitment; HM, high mixed degree of motor unit recruitment; F, full recruitment of motor units.

no apparent abnormalities in nerve conduction study and electromyography results (tables 1 and 2).

DISCUSSION

Vitamin E is one of the most widely distributed vitamins in foods, the richest sources being vegetable oils (soybean, corn, cottonseed, and safflower oils) and the products made from them. The absorption of tocopherols is dependent on a person's ability to digest and absorb fat. Bile is essential for the absorption. For maximal absorption, incorporation of the vitamin into mixed micelles is necessary.[10] The fat-soluble vitamins are particularly prone to deficiency during cholestasis because of the requirement of adequate bile flow for intraluminal solubilization of ingested lipids. Each of these vitamins may be poorly absorbed if any phase of fat digestion, absorption, or transport is interrupted.[2]

In general, patients with intrahepatic cholestatic syndromes have a more severe deficiency and are virtually refractory to oral standard supplementation of vitamin E because of deficient intraluminal concentration of bile acids. The most critical factor in vitamin E absorption is the intraluminal concentration of bile acids.[11] These patients can be treated with a water-soluble form of vitamin E, TPGS, which, when taken orally, forms micelles at low concentrations, and thus bile acids are not required in the intestinal lumen.[12,13] The use of TPGS vitamin E to solubilize and improve intestinal absorption of the other fat-soluble vitamins is a potentially simple means of correcting fat-soluble vitamin deficiencies in patients with chronic cholestasis when using available oral preparations of the other fat-soluble vitamins.[2]

Early recognition of vitamin E deficiency, regardless of etiology, is imperative, because treatment with vitamin E may arrest or reverse the progression of neurologic symptoms.[14] The reported patient developed neurologic syndromes suggestive of peripheral neuropathy more than 20 years after the onset of gastrointestinal symptoms and chronic hepatobiliary disease. Harding and colleagues[15] suggested a prolonged and severe deficiency of vitamin E may cause a central-peripheral distal axonopathy in humans. If neurologic disease secondary to vitamin E deficiency occurs, it is likely to be related to the duration and severity of the depletion. After the patients in Harding's report received treatment with vitamin E, their sensory nerve action potentials became normal but their deep tendon reflexes remained absent. Harding suggested that these findings may have been related to a persisting central axonopathy with interruption of the reflex arc at a site proximal to the dorsal root ganglia.

In children with prolonged deficiency of vitamin E, degenerative neuromyopathy begins within the first 2 years of life. In adults with cholestasis, however, stores may not be depleted until 1 to 2 years of vitamin E malabsorption has occurred, and an additional 5 to 10 years may pass before the mature nervous system degenerates.[2] Jeffrey and coworkers[16] reported that 44% of patients with primary biliary cirrhosis and 32% with other forms of chronic cholestatic liver disease had plasma vitamin E concentrations of $<12.3\mu mol/L$. Their study examined five peripheral neuropathies in 12 patients with primary biliary cirrhosis and severe vitamin E deficiency.

Rosenblum and associates[17] found degeneration of the posterior columns with some focal loss of nerve cells in the posterior root ganglia. There was mild loss of large myelinated fibers in the sural nerves, but the proximal nerve trunks were normal. Towfighi[18] reported that vitamin E–deficient rats had degenerative axonal changes in the subcutaneous nerves, pacinian corpuscles, and muscle spindles with relative sparing of the sciatic nerve and roots. Nelson and coworkers[19] described neuropathologic findings in monkeys. The most striking abnormality was loss of axons and myelin in the dorsal columns. This abnormality was most severe in the rostal part of the spinal cord. There was slight fiber loss in the dorsal roots. Degeneration of small numbers of neurons was noted in the dorsal root ganglia. In the sural nerve there was marked loss of myelinated fibers, predominantly those of large diameter, which increased in severity in a proximal to distal direction. They postulated that this degeneration resulted from axonal membrane injury and then developed as a distal and "dying back" type of axonopathy.[5,19]

The first detectable neurologic abnormality resulting from vitamin E deficiency in humans is decreased sensory perception.[20] Einarson[21] described the earliest stage of progressive neuromuscular syndrome in chronic vitamin E–deficient rats as clumsiness and muscle atrophy, followed by progressive weakness and sensory abnormalities. Other abnormalities reported to result from vitamin E deficiency include hyporeflexia or areflexia, trunkal ataxia, limb ataxia, ophthalmoplegia, decreased proprioception, decreased vibratory sensation, proximal muscle weakness, decreased light-touch sensation, decreased pain sensation, dysarthria, pes cavus, and scoliosis.[22]

Patients younger than 3 years old with neurologic dysfunction have tended to show a prompt response to TPGS therapy with reversal of abnormalities in 6 to 12 months. Older patients, however, particularly those with severe, handicapped symptomatology, have had a more limited, gradual improvement or only stabilization of dysfunction.[23] Verification of the pathogenetic role of vitamin E deficiency in neuromuscular disorders has been provided by the consistent stabilization or improvement in neurologic symptomatology,[22,24] peripheral nerve electrophysiology,[25,26] and evoked potentials[27] following correction of the vitamin E deficiency state. Cynamon and colleagues[26] reported prolonged latencies and decreased sensory action potentials of sural nerves in patients with vitamin E deficiency. Werlin and associates[28] described the preservation of normal or near-normal nerve conduction velocities in children with severe clinical conditions caused by vitamin E deficiency, and believe that this finding suggests that vitamin E deficiency affects the axon more prominently than the myelin sheath. Brin and associates[20] reported prominent abnormalities in sensory nerve conduction study findings (65%) and H-reflexes in patients with vitamin E–deficient neuropathy. Their findings show that electrophysiologic abnormalities in vitamin E–deficient neuropathy primarily result from axonal pathology.

In this case, we examined electrophysiologic recovery from

vitamin E–deficient neuropathy in a patient with chronic hepatobiliary disease. Nerve conduction studies suggest that axonal degeneration rather than demyelination is the primary sensory abnormality in vitamin E–deficient neuropathy. We conclude that vitamin E–deficient neuropathy is reversible and that electrophysiologic recovery can occur with water-soluble vitamin E therapy.

References

1. Dimitrov NV, Meyer C, Gilliland D, Ruppenthal M, Chenoweth W, Malone W. Plasma tocopherol concentrations in response to supplemental vitamin E. Am J Clin Nutr 1991;53:723-9.
2. Sokol RJ. Fat-soluble vitamins and their importance in patients with cholestatic liver diseases. Gastroenterol Clin North Am 1994;23:673-705.
3. Sokol RJ, Heubi JE, Iannaccone S, Bove KE, Balistreri WF. Mechanism causing vitamin E deficiency in children with chronic cholestasis. Gastroenterology 1983;85:1172-82.
4. Traber MG, Cohn W, Muller DP. Absorption, transport and delivery of tissues. In: Packer L, Fuchs J, editors. Vitamin E in healthy and disease. New York: Marcel Dekker, Inc.; 1993. p. 35-51.
5. Muller DPR, Lloyd JK, Wolff OH. Vitamin E and neurological function. Lancet 1983;1:225-7.
6. Binder HJ, Solitaire GB, Spiro HM. Neuromuscular disease in patients with steatorrhoea. Gut 1967;8:605-11.
7. Kayden HJ, Traber MG. Absorption, lipoprotein transport and regulation of plasma concentrations of vitamin E in humans. J Lipid Res 1993;34:343-58.
8. Sokol RJ, Heubi JE, Butler-Simon N, McClung HJ, Lilly JR, Silverman A. Treatment of vitamin E deficiency during chronic childhood cholestasis with oral *d*-α-tocopheryl polyethylene glycol-1000 succinate. Gastroenterology 1987;93:975-85.
9. Traber MG, Schiano TD, Steephen AC, Kayden HJ, Shike M. Efficacy of water-soluble vitamin E in the treatment of vitamin E malabsorption in short-bowel syndrome. Am J Clin Nutr 1994;59:1270-4.
10. Bieri JG, Corash L, Hubbard VS. Medical uses of vitamin E. N Engl J Med 1983;308:1063-71.
11. Muller DPR, Harries JT, Lloyd JK. The relative importance of the factors involved in the absorption of vitamin E in children. Gut 1974;15:966-71.
12. Sokol RJ, Heubi JE, Iannaccone S, Bove KE, Balistreri WF. Mechanism causing vitamin E deficiency during chronic childhood cholestasis. Gastroenterology 1983;85:1172-82.
13. Traber MG, Kayden HJ, Green JB, Green MH. Absorption of water-miscible forms of vitamin E in a patient with cholestasis and in rats. Am J Clin Nutr 1986;44:914-23.
14. Jackson CE, Amato AA, Barohn RJ. Isolated vitamin E deficiency. Muscle Nerve 1996;19:1161-5.
15. Harding AE, Muller DPR, Thomas PK, Willison HJ. Spinocerebellar degeneration secondary to chronic intestinal malabsorption: a vitamin E deficiency syndrome. Ann Neurol 1982;12:419-24.
16. Jeffrey GP, Muller DPR, Burroughs AK, Matthews S, Kemp C, Epstein O, et al. Vitamin E deficiency and its clinical significance in adults with primary biliary cirrhosis and other forms of chronic liver disease. J Hepatol 1987;4:307-17.
17. Rosenblum JL, Keating JP, Prensky AL, Nelson JS. A progressive neurologic syndrome in children with chronic liver disease. N Engl J Med 1981;304:503-8.
18. Towfighi J. Effects of chronic vitamin E deficiency on the nervous system of the rat. Acta Neuropathol (Berl) 1981;54:261-8.
19. Nelson JS, Fitch CD, Fischer VW, Brown GO, Chou AC. Progressive neuropathologic lesions in vitamin E-deficient rhesus monkeys. J Neuropathol Exp Neurol 1981;40:166-86.
20. Brin MF, Pedley TA, Lovelace RE, Emerson RG, Gouras PG, MacKay C, et al. Electrophysiologic features of abetalipoproteinemia: functional consequences of vitamin E deficiency. Neurology 1986;36:669-73.
21. Einarson L. Criticizing review of the concepts of the neuromuscular lesions in experimental vitamin E deficiency, preferably in adult rats. Acta Psychiatr Scand 1975;78:9-76.
22. Sokol RJ, Guggenheim MA, Iannaccone ST, Barkhaus PE, Millder C, Silverman A, et al. Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. N Engl J Med 1985;313:1580-6.
23. Sokol RJ, Butler-Simon N, Heubi JE, Iannaccone ST, McClung HJ, Accurso F, et al. Vitamin E deficiency neuropathy in children with fat malabsorption: studies in cystic fibrosis and chronic cholestasis. Ann N Y Acad Sci 1989;570:156-69.
24. Alagille D. Vitamin E deficiency in responsible for neurologic abnormalities in cholestatic children. J Pediatr 1985;107: 422-5.
25. Guggenheim MA, Ringel SP, Silverman A, Grabert BE. Progressive neuromuscular disease in children with chronic cholestasis and vitamin E deficiency: diagnosis and treatment with alpha tocopherol. J Pediatr 1982;100:51-8.
26. Cynamon HA, Milov DE, Valenstein E, Wagner M. Effect of vitamin E deficiency on neurologic function in patients with cystic fibrosis. J Pediatr 1988;113:637-40.
27. Cynamon HA, Norcross K, Isenberg JN. Evoked potential abnormalities in children with chronic cholestasis. Hepatology 1988;8: 1596-601.
28. Werlin SL, Harb JM, Swick H, Blank E. Neuromuscular dysfunction and ultrastructural pathology in children with chronic cholestasis and vitamin E deficiency. Ann Neurol 1983;13:291-6.

Supplier

a. Twin Laboratories, Inc., Ronkonkoma, NY 11779.