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Nutritional Neuropathy

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Author: **R Andrew Sewell, MD,** Mental Illness Research, Education, and Clinical Center (MIRECC) Fellow, Veterans Affairs Connecticut Health Care System, Yale University School of Medicine

R Andrew Sewell is a member of the following medical societies: American Academy of Neurology, American Headache Society, American Pain Society, American Psychiatric Association, and Massachusetts Medical Society

Coauthor(s): **Lawrence D Recht, MD,** Professor of Neurology and Neurosurgery, Department of Neurology and Clinical Neurosciences, Stanford University Medical School

Editors: **Milind J Kothari, DO,** Professor and Vice-Chair for Education and Training, Department of Neurology, Pennsylvania State University College of Medicine; Consulting Staff, Department of Neurology, Hershey Medical Center; **Francisco Talavera, PharmD, PhD,** Senior Pharmacy Editor, eMedicine; **Glenn Lopate, MD,** Associate Professor, Department of Neurology, Division of Neuromuscular Diseases, Washington University School of Medicine; Chief of Neurology, St Louis ConnectCare, Consulting Staff, Barnes Jewish Hospital; **Selim R Benbadis, MD,** Professor, Director of Comprehensive Epilepsy Program, Departments of Neurology and Neurosurgery, University of South Florida School of Medicine, Tampa General Hospital; **Nicholas Y Lorenzo, MD,** Chief Editor, eMedicine Neurology; Consulting Staff, Neurology Specialists and Consultants

Author and Editor Disclosure

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INTRODUCTION

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Background

The first study of the relationship between nutrition and peripheral neuropathy began in the 19th century, when polyneuropathy and heart failure from beriberi reached epidemic proportions. In 1897, Dr. Eijkman cured the disease in pigeons by feeding them the nutrient-rich rice husks that were stripped from the polished rice produced by the grain mills of the time. The mystery ingredient was christened "vitamine" in 1911, then changed to "thiamine" in 1936 when the sulfur-containing molecular structure was characterized. Since then, outbreaks of nutritional neuropathy have occurred in World War II prisoner-of-war camps, Jamaican sugar-cane plantations, and Cuba following the collapse of Soviet food support in the 1990s.

Pathophysiology

Neuropathies occur in 2 forms: an isolated deficiency (usually of a B vitamin) or a complex deficiency resulting from several concurrent metabolic disorders (usually including malabsorption). The mechanisms of the discrete deficiencies are described below.

Alcohol exposure

Ethanol intercalates into cell membranes, increasing membrane fluidity. Alcohol also affects many signal-transduction proteins, including ion channels, secondary messengers, neurotransmitters, neurotransmitter receptors, G proteins, chaperonins, and regulators of genetic expression.

Peripheral neuropathy is often the earliest symptom of chronic alcohol dependence, and generally occurs after consumption of at least 100 g/d for several years. Peripheral nerve damage results from 3 processes, and it is controversial which is the most important. The first is nutritional deficiency, especially thiamine deficiency, as ethanol interferes with thiamine absorption in the intestine. Other deficiencies may involve niacin, folate, or protein. The second is direct toxicity from abnormal products (eg, phosphatidyl ethanol, fatty acid ethyl esters) and from metabolites (eg, acetaldehyde that reacts with proteins to form adducts). The third is indirect toxicity (ie, neuropathy from hepatic dysfunction).

Likely, the direct toxic effects of ethanol and its metabolites are involved in the pathogenesis of the pure form of alcoholic neuropathy but this can be modified by a superimposed thiamine deficiency.

Thiamine deficiency

Thiamine (vitamin B_1) is found in wheat germ, or the outer layer of seeds, nuts, and most vegetables. Thiamine pyrophosphate is essential for the proper transfer of the aldehyde groups, and it is an essential coenzyme for glycolytic and pentose pathways of glucose metabolism. Four enzymes need thiamine: pyruvate dehydrogenase, a-ketoglutarate dehydrogenase, transketolase, and branched-chain a-ketoacid dehydrogenase.

Body tissues store about 30 mg but use about 1-2 mg daily. The United States recommended daily allowance (RDA) for men is 1.5 mg. Daily intake of less than 0.2 mg causes a discontinuous degeneration of the axonal sheath with subsequent impairment of the axon, producing a polyneuropathy in about 3 months. The vagal nerve is affected particularly, causing symptoms in the distributions of the cardiac, laryngeal, and recurrent nerves.

Thiamine deficiency can cause wet beriberi, for which congestive heart failure is the primary symptom, or dry beriberi, in which a peripheral neuropathy is the primary symptom, depending on the percentage of carbohydrates in the diet. Deficiencies preferentially affect the nervous and cardiac tissue because thiamine pyrophosphate is bound less strongly there than elsewhere.

Niacin deficiency

Niacin (vitamin B_3) is found in yeast, beef, pork, and chicken. The active form of this coenzyme, nicotinamide adenine dinucleotide (NAD), is essential for electron and acyl-group transfer in glycolysis. A deficiency of niacin causes pellagra. The US RDA for men is 20 mg.

Pyridoxine deficiency and excess

Pyridoxine (vitamin B_6) widely occurs in plant and animal tissues, such as muscle meats, liver, vegetables, and whole-grain cereals. Vitamin B_6 consists of pyridoxine, pyridoxal, and pyridoxamine. It is involved in primary carboxylation and transamination, playing a role in metabolizing tryptophan, glycine, serotonin, and glutamate, as well as sulfur-containing amino acids. Pyridoxine is used in the synthesis of both heme and g-aminobutyric acid (GABA). Deficiencies are usually associated with increased excretion due to isoniazid ingestion and cause a sensorimotor neuropathy and seizures. Pyridoxine deficiency is rarely associated with a vasculitic mononeuropathy multiplex. A high-protein diet increases pyridoxine requirements, for which the US RDA for men is 2 mg.

The toxic effect of long-term, excessive pyridoxine consumption on the dorsal root ganglions causes a pure sensory neuropathy. Pyridoxine inhibits methionine metabolism, causing an increase in S-adenosylmethionine, which in turn inhibits myelin synthesis. In general, exposure of 2 g/d is needed to cause the neuropathy, but cases due to longstanding use of as little as 200 mg/d have been reported.

Cyanocobalamin deficiency

Cyanocobalamin (vitamin B_{12}) is found in meats, especially liver and kidney, and in cheese, milk, eggs, and fish. This inactive precursor is converted into 2 active metabolites: methylcobalamin and adenosylcobalamin. Methylcobalamin is essential for folate metabolism and for the formation of choline-containing phospholipids, which are the building blocks of myelin. Adenosylcobalamin is required for the formation of succinyl coenzyme A, the lack of which causes impairment in the formation of neural lipids.

After its ingestion, cyanocobalamin binds with intrinsic factor secreted by parietal cells in the stomach, enabling it to resist proteolysis. Receptors in the distal ileum then facilitate digestion. The liver stores 4 mg of cyanocobalamin, representing a 3- to 6-year supply. Therefore, primary deficiencies are rare, except in strict vegetarians and nursing infants, but manifestations of cyanocobalamin deficiency occasionally complicate the presence of malabsorptive disorders. These lesions, which appear throughout the white matter, are a result of a focal disintegration of medullary sheath known as subacute combined degeneration. A single exposure to nitrous oxide may precipitate paresthesias in the hands and feet as well as features of a classic myeloneuropathy within days to weeks. The US RDA for men is 2 mg.

Pantothenic acid deficiency

Almost all foods contain this constituent of coenzyme A, the concentration of which in tissues is 10 times that of thiamine and 50% that of nicotinic acid. Deficiencies are rare because of this large amount of storage, though pantothenic acid has been implicated in the pathogenesis of burning-foot syndrome. The daily requirements are 6-10 mg.

Alpha-tocopherol deficiency

Alpha-tocopherol (vitamin E) is a lipid-soluble antioxidant. Its lack causes a syndrome resembling spinocerebellar degeneration, reversible in early stages but with devastating consequences if allowed to progress. The US RDA is 10 IU.

Gluten-sensitivity neuropathy (celiac disease)

Antibodies to gluten in wheat, barley, and oats in susceptible individuals also attack Purkinje cells and other neurons, leading to cerebellar ataxia, myoclonus, and neuropathy.

Multifactorial mechanism

This poorly characterized syndrome of neuropathy and visual and auditory deficits is common in prisoners of war camps and in undernourished populations of tropical countries. Also known as "camp foot," "Jamaican neuritis," "camp dizziness," "Strachan syndrome," and other names, the neuropathy is probably due to a deficiency of B vitamins. Sensorineural deafness is postulated to result from deficiency in riboflavin or B-complex vitamins, and the amblyopia, too, may be from a complex deficiency, as it sometimes does not resolve with vitamin B_{12} treatment alone.

Frequency

United States

About 10,000,000 (4%) Americans are dependent on alcohol. Because of this, alcohol is the most common cause of deficiency neuropathy. About 9-30% of people with alcoholism have clinically evident neuropathy, and more than 90% have electrophysiological evidence of neuropathy.

Approximately 4-15% of ambulatory elderly people (>65 y) will have cobalamin deficiency.

Nearly 10% of people taking isoniazid will have neuropathy.

The increasing incidence of obesity in the United States has led to increased rates of bariatric surgery and consequent malabsorption neuropathies.

International

Thiamine (vitamin B_1) deficiency is still endemic in the Far East; nutritional deficiencies and malnutrition are common in the developing nations.

Mortality/Morbidity

Morbidity and mortality rates vary by etiology.

Race

Racial differences in incidence are likely due to differing socioeconomic status and geographic location.

Sex

Alcoholic neuropathy affects men more than women, but women appear to be susceptible at lower doses.

Age

- The incidence of neuropathy due to alcohol dependence peaks at the age of 40 years, although the primary disease may become established decades earlier.
- Thiamine (vitamin B_1) deficiency predominantly occurs in adolescence and early adulthood.
- Children are particularly prone to pyridoxine deficiency, which becomes apparent within a few days of birth.

History

Peripheral neuropathies due to nutritional deficiencies have few individually characteristic signs but can be differentiated by observing other symptoms of the patient's underlying systemic disease. Neuropathies mostly affect the long fibers first, starting in the feet and progressing upward. Once they have progressed to the calf, symptoms may appear in the hands. Cyanocobalamin (vitamin B_{12}) deficiency occasionally manifests in the upper extremities.

- Alcohol neuropathy
  - This disease is characterized by paresthesias (decreased pain and temperature sensation in a stocking-glove distribution), pain, and weakness, especially in the feet but extending proximally to the arms, causing difficulty in climbing stairs and walking.
  - Autonomic symptoms are less common than those listed above, but include GI dysmotility, urinary or fecal

incontinence, and abnormal sweat patterns.

- The neuropathy may be seen in conjunction with Wernicke encephalopathy (ie, ophthalmoplegia, ataxia, encephalopathy) or Korsakoff syndrome (ie, amnestic dementia).

- Thiamine (vitamin B_1) deficiency
  - Dry beriberi is characterized by severe burning dysesthesias (feet more than hands), weakness and wasting (distal more than proximal), trophic changes (shiny skin, hair loss), and acrodistal sensory loss in a graded fashion typical of dying back polyneuropathies.
  - Some patients do not become symptomatic, possibly because they are absorbing thiamine produced by bacteria in the large intestine. However, one half become symptomatic by 7 weeks; by 15 weeks, axonal changes start to appear histologically.
  - The neuropathy begins with fatigue and loss of sensation, pain, and heaviness in the legs. Then, pretibial edema develops, along with glove-and-stocking paresthesias and difficulty with tasks such as climbing stairs and standing on one leg.
  - If the thiamine deficiency is long standing, muscles on the dorsum of the feet atrophy and paralysis can ensue.
  - Difficulty with talking or swallowing may also be noted.

- Niacin (vitamin B_3) deficiency
  - Pellagra is characterized by the *3 D*s, which are (1) dermatitis, ie, hyperkeratotic skin lesions, particularly on hands, feet, face, and neck (sun-exposed regions); (2) diarrhea; and (3) dementia, ie, peripheral neuropathy and other CNS signs, such as depression, excitation, seizures, insomnia, dizziness, cog-wheeling of the extremities, tremor, loss of hearing, tingling fingers, muscle tenderness, and bilateral symmetric glove-and-stocking numbness.
  - Polyneuropathy is not always associated with pellagra and may be related to accompanying thiamine or pyridoxine deficiency. Therefore, it should be considered an accompanying rather than guiding symptom. It is characterized by acrodistal sensory excitation, the itching and burning in the hands, feet, and trunk, and it sometimes manifests as hydromania, or the compulsion to immerse oneself in cold water.
  - The dysesthesias progress proximally to the knees, thighs, and hips, after which weakness in the legs becomes manifest.
  - Paresis is rare, but bulbopontine symptoms can ensue, with abnormalities of the cranial nerves, especially the vestibular, acoustic, and ocular nerves (where symptoms manifest as optic atrophy or amblyopia), as well as seizures.
  - Eventually, the initial peripheral excitation, erythema, and GI distress progress to cerebral and spinal defects.
  - Finally, marasmus, cachexia, macrocytic anemia, and coma develop.

- Pyridoxine (vitamin B_6) deficiency or excess
  - Deficiency must be suspected any time a sensory polyneuropathy occurs after hyperesthesia-causalgia syndrome.
  - First, bilateral numbness and tingling begin in the distal feet. This proceeds proximally up the feet and legs, occasionally appearing in the fingers and hands. Then pain becomes prevalent in these areas, and symptoms can include a burning sensation in the feet.
  - In rare cases, patients experience loss of power in the legs, in which sensory loss is greater than motor loss; the etiology is axonal loss.

- One week after the removal of vitamin B_6 from the diet, levels of xanthurenic acid increase and levels of pyridoxine decrease in the urine. At 3 weeks, EEG abnormalities manifest, and tonic-clonic seizures refractory to anticonvulsants may follow.
- The 4 main symptoms and signs are as follows:
  - Cutaneous mucosal symptoms - Glossitis, conjunctivitis, cheilosis
  - CNS symptoms - Lethargy, decreased level of consciousness, anorexia, vomiting, seizures
  - Ascending sensory polyneuropathy
  - Anemia - Lymphopenia with eosinophilia
- Neuropathy due to toxicity occurs 1 month to 3 years after the individual starts excessive consumption.

- Cyanocobalamin (vitamin B_{12}) deficiency
  - About 80% of all cases are due to pernicious anemia, and another 10% are due to *achlorhydria*. Exposure to nitrous oxide can suddenly precipitate the deficiency, which should be considered in any patient who develops postoperative paresthesias.
  - The disease predominantly affects the spinal cord; therefore, separating the painful sensory and sensorimotor paresthesias of the peripheral neuropathy from the symptoms of spinal cord involvement is difficult.
  - Presentations vary greatly among patients.
  - The symmetric glove-and-stocking paresthesias, or tingling in the distal aspect of the toes, numbness, coldness, a pins-and-needles feeling, and occasional feelings of swelling or constriction, are slowly progressive and insidious. Symptoms progressing up the legs, occasionally affect the fingers, and culminate in weakness and spasticity.
  - In late stages, signs include moderate muscular wasting, optic atrophy, sphincter dysfunction, and mental disturbances. Examples of these disturbances are mild dementia (which is often the first symptom and clinically indistinguishable from other dementias), disorientation, depression, psychosis, and persecutory delusions.
  - The hematologic manifestation of anemia, if present, can cause weakness, light-headedness, vertigo, tinnitus, palpitations, angina, heart failure, cardiomegaly, pallor, tachycardia, and hepatosplenomegaly.
  - GI symptoms include a sore, beefy red tongue and anorexia.
  - If left untreated, the gait becomes ataxic, followed by paraplegia with spasticity and contractures.
  - The subacute combined degeneration that develops results in a severe myelopathy, involving posterior columns and lateral corticospinal tracts, with other manifestations including optic (retrobulbar) neuropathy, sensorimotor polyneuropathy, and dementia.

- Pantothenic acid deficiency: This manifests as painful burning paresthesias in the feet, ataxia, and hyperreflexia, followed by weakness, fatigue, apathy, and psychiatric disturbances 5-8 weeks later.

- Alpha-tocopherol (vitamin E) deficiency
  - This syndrome resembles Friedreich ataxia. Symptoms include hyporeflexia progressing to areflexia, decreased proprioception and vibration sense with preserved pain and temperature senses, distal muscular weakness progressing to ataxia, dysphagia, and cardiac problems, and nyctalopia (night blindness). Nystagmus, ophthalmoplegia, and blindness, and dementia follow.

- Symptoms vary with etiology. Patients with isolated vitamin E deficiency syndrome tends to present without the hyporeflexia, and deficiency from abetalipoproteinemia manifests with increased eye problems, in contrast with deficiency from cholestatic disease, which tends to spare the eye but cause increased psychiatric and behavioral problems.

- Folate deficiency: The symptoms of folate deficiency are indistinguishable from those of cobalamin (vitamin B_{12}) deficiency, though the dementia tends to be more prominent.

- Hypophosphatemia
  - Invariably found in patients on total parenteral nutrition, this deficiency causes tingling paresthesias in the tongue, fingers, and toes but can progress to severe weakness and areflexia, sensory loss, and cranial neuropathies.
  - It can resemble the Guillain-Barré syndrome.
  - Patients may have gluten sensitivity.
  - Neurologic manifestations can include ataxia, myoclonus, myopathy, myelopathy, dementia, and a peripheral neuropathy that can include sensorimotor axonal neuropathy, axonal motor and mononeuropathy multiplex.

- Copper deficiency (usually following bariatric surgery, associated with myelopathy and a sensory neuropathy)

- Multifactorial disease
  - This paresthesia-causalgia syndrome (ie, acrodynia or burning-foot syndrome) escalates from a mild paresthesia to painful burning and freezing sensations in the feet, prominent at night, relieved with exercise. This disease may mask sensory deficits, especially those on the soles of the feet.
  - Tobacco-alcohol amblyopia is a slowly progressive symmetrical visual field loss often described as a central haze or cloud. There is no pain, photopsia, or other positive symptoms, but loss of color vision (especially red) is more profound than the loss of visual acuity.
  - Less common is mild-to-moderate unilateral or bilateral hearing loss with tinnitus or vertigo.
  - Hoarseness and other laryngeal symptoms are equally rare.

Physical

Several physical findings can provide clues to the etiology of the nutritional neuropathy.

- Mouth: Glossitis suggests cyanocobalamin (vitamin B_{12}) deficiency (see Media file 1); glossitis and cheilosis suggest pyridoxine (vitamin B_6) deficiency; gingivitis, stomatitis, and glossitis, niacin (vitamin B_3) deficiency.

- Skin: Nasolabial seborrhea suggests pyridoxine (vitamin B_6) deficiency; pellagrous skin rash, niacin (vitamin B_3) deficiency; and hyperpigmentation, cobalamin (vitamin B_{12}) deficiency.

- Cardiovascular: CHF suggests thiamine (vitamin B_1) deficiency.

- Hematologic: Megaloblastic anemia suggests a cobalamin (vitamin B_{12}) or folate deficiency. Hypochromic anemia is usually iron deficiency but also can represent a pyridoxine vitamin (B_6) deficiency.

- Findings in specific syndromes include the following:
  - Alcohol neuropathy
    - This is characterized by decreased pain and temperature sensation in a stocking-glove distribution,

distal muscle weakness and atrophy (legs worse than arms) with stasis pigmentation and plantar ulcerations, wrist and foot drop, hyporeflexia with absent Achilles reflex, and antalgic gait.

- The skin may be dry and scaly with rhinophyma (alcohol nose).
- Hepatomegaly, jaundice, or ascites may result from concurrent liver dysfunction.
- Alcohol neuropathy frequently is associated with entrapment or pressure neuropathies, particularly ulnar and peroneal, which may be superimposed on the polyneuropathy.
- Charcot joints and Wernicke-Korsakoff syndrome may also be present.

- Thiamine (vitamin B_1) deficiency (beriberi)
  - About 70% of patients have a polyneuropathy; of those, 20% have only motor involvement; 50%, motor-sensory involvement; and 30%, only sensory involvement.
  - It is both subchronic and chronic; presentation includes paresthesias and numbness, fasciculations and cramps, followed by dorsiflexor weakness with a stepping gait. Finally, bilateral lower-extremity paraplegia develops.
  - In about 30% of patients, the neuropathy spreads to the proximal muscles of the pelvic girdle, to the trunk, and to the upper extremities.
  - The patellar and Achilles tendon reflexes are decreased.
  - Cranial nerve manifestations include retrobulbar optic neuropathy, hoarseness, dysphagia, and tachycardia from vagal involvement and even bilateral facial paralysis in some cases.
  - In rare cases, an acute paraplegic form results in anorexia and vomiting. In a day or two, rapidly progressive paralysis ascends from legs to arms and shoulder girdle. Death from cardiac insufficiency follows within 2 days.

- Niacin (vitamin B_3) deficiency
  - Patients present with decreased proprioception and vibratory sense, weakness in legs with some fasciculations and cramping, Babinski reflexes equivocal or positive.
  - Paresis is rare, deep tendon reflexes are decreased in 10-20% but increased in most.
  - Simultaneous psychiatric disorders, extrapyramidal symptoms, cranial nerve dysfunctions, and seizures ultimately result.

- Pyridoxine (vitamin B_6) deficiency
  - The presentation includes seborrheic dermatitis, cheilosis, glossitis, nausea, vomiting, weakness, and dizziness.
  - Neurologic examination shows decreased proprioception and vibration sense with spared pain and temperature sensations; normal strength; decreased or absent Achilles reflex and decreased patellar reflex.
  - Ataxia, if present, is sensory.

- Pyridoxine toxicity
  - Pyridoxine toxicity can also cause a neuropathy.
  - Acute high-dose (180 g) intoxication causes a sensory neuronopathy. Clinical manifestations

include diffuse paresthesias, proximal and distal sensory loss, sensory ataxia, and autonomic dysfunction. Recovery tends to be poor.

- Long-term low dosages (0.2-10 g/d) cause a milder distal sensory neuropathy, which presents with distal paresthesias and numbness.
- Recovery is usually good after pyridoxine is stopped.

- Folate deficiency: Patients present with subacute combined degeneration, sensorimotor polyneuropathy, and dementia.
- Cyanocobalamin (vitamin B_{12}) deficiency: The presentation includes a number of neurologic findings.
  - Corticospinal tract abnormalities include spasticity. About 50% of patients lack an Achilles reflex, some have no patellar reflex, some have a bilateral positive Babinski sign, and hyperreflexia is rare.
  - Posterior column abnormalities - Decreased vibration, temperature, and proprioception senses (lower extremities); sensory ataxia; positive Romberg sign in later stages
  - Peripheral neuropathy - Moderately severe to severe, with muscular atrophy and weakness in later stages
  - Behavioral and personality changes, particularly depression
- Nutritional amblyopia: Patients present with decreased visual acuity and sometimes bilateral field defects with central or cecocentral scotomas. Early on, the optic discs show no change or papillitis on funduscopic examination. Later, the discs become pallid (see Media file 2).
- Nutritional sensorineural deafness: The presentation includes mild-to-moderate unilateral or bilateral hearing loss.

Causes

- Thiamine (vitamin B_1) deficiency
  - Malabsorption from pyloric stenosis, gastroenterostomy, ulcerative colitis, dysentery, steatorrhea, gastritis, pancreatitis, or prolonged diarrhea
  - Leigh disease (subacute necrotizing encephalomyelopathy)
  - Thiamine-responsive acidosis
  - Abnormal pyruvate dehydrogenase
  - Decreased dietary intake as in alcohol dependence
  - Nothing by mouth (NPO) status when patients receive intravenous fluids without thiamine supplementation
  - Hyperemesis of pregnancy
  - Acute postgastric reduction surgery
  - Dialysis
  - Refeeding syndrome

- Chastek paralysis from ingestion of raw fish containing thiaminidases
- Infection with *Bacillus thiaminolyticus*

- Niacin (vitamin B_3) deficiency
  - Inadequate intake (eaters of a predominantly maize diet, pregnant or lactating women whose requirements have increased, those who are alcohol dependent and have poor nutrition)
  - Hartnup disease
  - Malabsorption syndromes

- Pyridoxine (vitamin B_6) deficiency
  - Deficient infant formula
  - Deficient intake (probably due to preferential ethanol ingestion)
  - Increased metabolic demands as in pregnancy, febrile states, and after abdominal surgery
  - Malabsorption
  - Medications, such as isoniazid (the most likely etiology), hydralazine, cycloserine, penicillamine, desoxypyridoxine, and oral contraceptives
  - Rare genetic disorders, such as pyridoxine dependency, which is evident within a few days of birth

- Cyanocobalamin (vitamin B_{12}) deficiency
  - Pernicious anemia
  - Gastrectomy or gastric mucosa atrophy
  - Chronic pancreatitis (40% manifest deficiency, as cyanocobalamin binds proteins other than intrinsic factor that are not being broken down by pancreatic proteases)
  - Distal ileal disease (inflammatory bowel syndrome or neoplasm)
  - Infections (eg, tropical sprue, regional enteritis, *Diphyllobothrium latum* tapeworm, blind-loop syndrome)
  - Congenital malabsorption (Imerslund-Gräbeck disease)

- Pantothenic acid: A primary deficiency almost never occurs; therefore, symptoms must be presumed to be from secondary deficiency

- Alpha-tocopherol (vitamin E)
  - Malabsorption syndromes, such as (1) Crohn disease, (2) Bassen-Kornzweig disease (abetalipoproteinemia), (3) pancreatic dysfunction (cystic fibrosis), (4) vitamin E transporter deficiency, and (5) chronic cholestatic hepatobiliary disease (eg, idiopathic neonatal hepatitis, familial cholestatic syndromes, intrahepatic bile duct disease, extrahepatic biliary atresia)
  - Short-bowel syndrome
  - Total parenteral nutrition
  - Other malabsorption syndromes

- Folic acid deficiency
  - Poor intake (eg, alcohol dependence, pregnancy)
  - Malabsorption syndromes
  - Medications (particularly phenytoin)
- Bariatric surgery can lead to malnutrition-related mononeuropathy, radiculoplexus neuropathy, and sensory-predominant polyneuropathy. The weakness is often accompanied by hyporeflexia and vomiting.

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Guillain-Barre Syndrome in Childhood
HIV-1 Associated Distal Painful Sensorimotor Polyneuropathy
HIV-1 Associated Multiple Mononeuropathies
Leprosy
Mercury
Polyarteritis Nodosa
Sarcoidosis and Neuropathy
Systemic Lupus Erythematosus
Thyroid Disease

Other Problems to be Considered

Hartnup disease - Symptoms resembling niacin deficiency
Diphyllobothriasis, toxic amblyopia, or Leber optic neuropathy - Amblyopia similar to that of nutritional deficiencies
Paraneoplastic sensory neuropathy - Especially in patients with clinically significant weight loss

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Lab Studies

- The neuropathy first must be characterized as a polyneuropathy, mononeuropathy, mononeuropathy multiplex disease, or plexopathy; motor, sensory, sensorimotor, motor-sensory, or autonomic; acute or chronic; and of demyelinating or axonal pathophysiology. Readily apparent clues in the history can often suggest that the peripheral neuropathy might be secondary to nutritional problems; they are as follows:
  - Excessive consumption of alcohol
  - History of bariatric surgery, especially gastrectomy and intestinal shortening
  - History of GI syndromes indicating a predisposition toward malabsorption

- History of using medications known to be associated with a vitamin deficiency (e.g., isoniazid)

- Once the neuropathy is suspected to be nutritional in origin, the physician should first assess a possible vitamin B_{12} deficiency (remembering that a CBC is not a good indicator). Documenting other B vitamin deficiencies is not as important because treatment replaces these vitamins anyway.

- If history—which is the key to diagnosing a nutritional neuropathy—and physical are unrevealing, check CBC, urinalysis, thyroid-stimulating hormone (TSH), glucose, renal and hepatic functions, vitamin B_{12} level, erythrocyte sedimentation rate (ESR), and serum protein electrophoresis, then order other tests as needed. Electrophysiologic findings can confirm the impression of polyneuropathy but rarely provide the diagnosis.
  - Alcohol neuropathy: CBC may show low platelet counts and a megaloblastic anemia due to decreased folate levels.
  - Thiamine (vitamin B_1) deficiency: A serum thiamine (vitamin B_1) level is not a good index because it responds quickly to dietary supplementation and because it is a poor indicator of total body stores. Urinary excretion of <65 mg/g of creatinine is abnormal. A pyruvate level of >1 mg/dL is a reliable indicator of deficiency. The best test is erythrocyte transketolase activity; a concentration of <0.017 U/dL indicates deficiency.
  - Pyridoxine (vitamin B_6) deficiency: The CBC shows a microcytic, hypochromic anemia with normal iron levels. Serum pyridoxine levels are <25 mg/mL, and serum homocysteine and cysathioprine values should be elevated. A tryptophan-loading test (not commonly performed) reveals urinary xanthurenic acid excretion of >50 mg/d.
  - Folate deficiency: Serum folate levels are low.
  - Niacin (vitamin B_3) deficiency: Urinary excretion of *N*-methylnicotinamide + *N*-methyl-6-pyridone-3-carboxamide is <2 mg, or urinary excretion of *N*-methylnicotinamide is <0.5 mg/g creatinine. Performing a stress test is possible by giving niacin 10 mg and tryptophan 100 mg. If urinary excretion of niacin metabolites is <3 mg, a deficiency is present.
  - Cyanocobalamin (vitamin B_{12}) deficiency: The CBC may show mean corpuscular volume (MCV) >110 fL (ie, macrocytic anemia), anisocytosis, poikilocytosis, and large and oval erythrocytes with decreased reticulocyte, leukocyte, and platelet counts. However, the neuropathy may precede any hematologic abnormalities in 25% of patients. The serum cobalamin level is <10 mg/dL but may be normal, even in those with a tissue cobalamin deficit. Serum homocysteine and methylmalonic acid levels are elevated, as is urinary methylmalonic acid excretion. Serum holotranscobalamin II is deficient. Intrinsic factor antibodies are specific for pernicious anemia but not very sensitive (40% negative). The traditional Schilling test is now rarely used.
  - Pantothenic acid deficiency: Excretion is <1 mg/d.
  - Alpha-tocopherol (vitamin E) deficiency: The serum a-tocopherol (vitamin E) level is low, and the CBC shows acanthocytes. Normal serum a-tocopherol levels in an adult with symptoms consistent with Friedreich ataxia should prompt an investigation for an autosomal recessive defect in the tocopherol transporter protein gene on chromosome 8.
  - Hypophosphatemia: Serum phosphate level is <1 mg/dL.
  - Gluten-sensitive neuropathy: Anti-gliadin antibodies, either IgM or IgA should be present. 90% have HLA DQ2. Intestinal biopsy is abnormal in only 35%.

Imaging Studies

- Imaging studies are generally not useful. In thiamine deficiency, MRIs occasionally show abnormal signal intensity in periaqueductal gray matter and midline structures.

- Radiographs of chronic peripheral neuropathies are often consistent with the picture of a diabetic foot.

Other Tests

- Axonal loss manifests as a mild slowing of the nerve conduction velocity (NCV) with a disproportionate loss of amplitude. Demyelination, on the other hand, shows mild loss of amplitude with a disproportionate slowing of the NCV. In affected motor fibers, electromyography (EMG) shows fibrillations, positive sharp waves, and decreased motor unit potentials. EMG and NCV are useful to assess the degree of damage and monitor progression of the neuropathy.
    - Thiamine (vitamin B_1) deficiency: EMG and nerve conduction studies reveal a generalized axonal sensorimotor polyneuropathy with denervation of the distal lower extremity musculature; at times some subtle demyelinating features may be present.
    - Niacin (vitamin B_3): EMG and NCV show demyelination in mild cases and axonal degeneration in severe cases.
    - Alpha-tocopherol (vitamin E) deficiency: Peripheral nerve conduction findings are normal. Sensory evoked potentials are low or absent. Somatosensory evoked potentials show a delay in central conduction. EMG findings are normal.
- Sensorineural hearing loss: Audiometry shows high-tone hearing loss.
- Alcohol: The CSF protein level on lumbar puncture is normal or slightly elevated.

Histologic Findings

A biopsy is not indicated unless the diagnosis is in doubt. If so, biopsy is indicated only if the neuropathy is multifocal, if it is asymmetric, or if it produces multiple mononeuropathies. The best nerve to biopsy is the sural nerve, lateral to the lateral malleolus. In general, sural nerve biopsy is of limited use in differentiating various types of nutritional neuropathy, but it can help in distinguishing hereditary neuropathy, neuropathy caused by organic solvents, leprosy, amyloidosis, polyarteritis nodosa, or sarcoidosis, and it is occasionally useful in evaluating Guillain-Barré syndrome. Nutritional neuropathies can result in either demyelinating or axonal peripheral nerve pathology.

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TREATMENT

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Medical Care

If the neuropathy is due to thiamine deficiency in an alcohol-dependent patient, consider instituting an alcohol-withdrawal protocol and providing seizure prophylaxis if indicated.

Surgical Care

- Prevent trophic changes to the skin and ulceration of the feet with orthotics.
- Consider surgical prophylaxis of osseous deformities.

Consultations

Refer the patient to an orthopedic surgeon for evaluation of osseous deformities.

Diet

Establishing an exact nutritional deficiency is often difficult. Many etiologies are often present simultaneously, especially in patients with malnutrition. Nutritional supplements are relatively innocuous. Therefore, for many nutritional neuropathies, the treatment is empirical and establishes the diagnosis. The further the disease has progressed, the lower the likelihood of reversing the symptoms.

- Alcohol: Discontinue alcohol; give folate 1 mg intramuscularly (IM) once daily (qd) for 3 days and thiamine (vitamin B_1) 50 mg IM qd and/or 50 mg orally (PO) 3 times daily (tid) for 3 days followed by a maintenance dose of 5-10 mg PO qd.
- Thiamine (vitamin B_1) deficiency: Administer parenteral B-complex vitamins, then oral thiamine, 50 mg IM qd for 3 days or 50 mg PO tid for 3 days; the maintenance dose is 5-10 mg PO qd. A maintenance dose of 0.5 mg/100 kcal is required.
- Niacin (vitamin B_3) deficiency: The peripheral neuropathy of pellagra does not respond to niacin supplements alone; both niacin and pyridoxine must be added to the diet. Niacin causes a vasocutaneous flush; therefore, administer nicotinamide 100 mg IM or intravenously (IV), followed by 200 mg PO tid. The RDA is 11.3-13.3 niacin equivalents, so named because tryptophan is a niacin precursor such that 60 mg tryptophan is equivalent to 1 mg niacin. This RDA is increased in pregnant women and in those with diets high in leucine (eg, millet).
- Pyridoxine (vitamin B_6) deficiency: Treat with excessive amounts of pyridoxine. Be careful of competitive inhibition with thiamine.
- Cyanocobalamin (vitamin B_{12}) deficiency: Give cyanocobalamin (vitamin B_{12}) supplementation and treat the underlying disease responsible for the deficiency state. Administer IM injections 1 mg/day for 1 week followed by 1 mg/week for 1 month. If malabsorption is the etiology, prescribe 1 mg/mo for life. Oral supplementation of 1 mg/d is acceptable if the integrity of the GI tract is preserved; this yields an absorption of 10 mcg/d.
- Folate deficiency: Give 1 mg PO qd. Do not give folate until cyanocobalamin (vitamin B_{12}) deficiency has been positively excluded. Folate corrects the hematologic abnormalities but worsen the neurologic dysfunction.
- Alpha-tocopherol (vitamin E) deficiency: Treatment varies depending on the cause, as follows:
  - Cystic fibrosis - 5-10 IU/kg qd
  - Cholestatic disease - 15-25 IU/kg qd
  - Abetalipoproteinemia - 100-200 IU/kg qd in divided doses with vitamin A 15,000-20,000 IU qd
  - Short bowel syndrome - 200-3600 IU qd
  - Vitamin E transporter deficiency - 800-3500 IU qd
- Gluten sensitivity: The ideal management is unclear, but a gluten-free diet appears prudent.
- Malnutrition: Thiamine replenishment alone is usually not sufficient to cause resolution of the symptoms; increase the protein in the diet slowly to 1.5-2 g/kg body weight qd.

Activity

Physical therapy is recommended to prevent joint contractures. Therapy consists of daily exercises though full range of motion, the use of splints to prevent foot drop, and the use of orthotics to minimize ulceration at denervated pressure points.

The goals of pharmacotherapy are to reduce morbidity and prevent complications.

Drug Category: *Vitamins*

To treat a nutritional neuropathy, replacing the deficient nutrients is necessary. This may involve administration of folate, thiamine (vitamin B_1), nicotinamide, pyridoxine (vitamin B_6), cyanocobalamin (vitamin B_{12}), alpha-tocopherol (vitamin E), vitamin A, or protein.

Drug Name	Thiamine (Thiamilate)
Description	For thiamine deficiency syndromes.
Adult Dose	50 mg IM qd for 3 d or 50 mg PO tid for 3 d, then maintenance dose of 5-10 mg PO qd
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	None reported
Pregnancy	A - Fetal risk not revealed in controlled studies in humans
Precautions	Sensitivity reactions (intradermal test-dose recommended if sensitivity suspected); deaths have resulted from IV use; administer before or with dextrose-containing fluids in suspected thiamine deficiency

Drug Name	Niacinamide (Vitamin B_3)
Description	Source of niacin used in tissue respiration, lipid metabolism, and glycogenolysis.
Adult Dose	100 mg IV/IM then 200 mg PO tid
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; active liver disease or unexplained, significant increases in AST and ALT levels; large doses of niacin, especially sustained release, associated with severe hepatotoxicity; definite and recent history of peptic ulcer

	disease can reactivate ulcers
Interactions	May potentiate effects of ganglion-blocking and vasoactive drugs, resulting in postural hypotension; may be inactivated by bile-acid sequestrants (colestipol, cholestyramine)—wait 4-6 h before ingestion
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus
Precautions	Caution in those with gallbladder disease, diabetes, or predisposition to gout; monitor blood glucose level; may elevate uric acid levels; pregnancy category C at doses above RDA

Drug Name	Cyanocobalamin (Crystamine)
Description	Deoxyadenosylcobalamin and hydroxocobalamin are active forms of vitamin B_{12} in humans. Vitamin B_{12} synthesized by microbes but not humans or plants. Vitamin B_{12} deficiency may result from intrinsic factor deficiency (pernicious anemia), partial or total gastrectomy, or diseases of distal ileum.
Adult Dose	1 mg qd IM for 1 wk then 1 mg/wk for 1 mo Maintenance dose: 1 mg qmo for life
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity; hereditary optic nerve atrophy
Interactions	None reported
Pregnancy	A - Fetal risk not revealed in controlled studies in humans
Precautions	Severe hypokalemia may result in vitamin B_{12}-megaloblastic anemia (may be fatal) due to increased cellular potassium requirements when anemia corrects

Drug Name	Folate (Folvite)
Description	Important cofactor for enzymes used to produce RBCs.
Adult Dose	1 mg PO qd
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	May decrease phenytoin to subtherapeutic levels, increasing seizure frequency
Pregnancy	A - Fetal risk not revealed in controlled studies in humans
Precautions	Benzyl alcohol present in some products as preservative; associated with fatal gasping syndrome in premature infants; resistance may occur with alcoholism and deficiencies of other vitamins; do not administer until cyanocobalamin (vitamin B-12) deficiency ruled out

Drug Name	Alpha-tocopherol (Vita-Plus E Softgels, Vitec, Aquasol E)
Description	Protects polyunsaturated fatty acids in membranes from attack by free radicals and protects RBCs against hemolysis.
Adult Dose	Cystic fibrosis: 5-10 IU/kg PO qd Cholestatic disease: 15-25 IU/kg PO qd Abetalipoproteinemia: 100-200 IU/kg in divided doses with 15,000-25,000 IU PO qd of vitamin A Short bowel syndrome: 200-3600 IU PO qd Isolated familial vitamin E deficiency: 800-3500 IU PO qd
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity

Interactions	Mineral oil decreases absorption of vitamin E; vitamin E delays absorption of iron and increases effects of anticoagulants
Pregnancy	A - Fetal risk not revealed in controlled studies in humans
Precautions	Large doses of vitamin E is pregnancy category C; vitamin E may induce vitamin K deficiency; necrotizing enterocolitis may occur with large doses

Drug Name	Multiple vitamins (MVI-12, Cernevit-12)
Description	Dietary supplement.
Adult Dose	MVI-12: 10 mL/24h IV Cernevit: 5 mL/24h IV
Pediatric Dose	MVI-12 <12 years: 5 mL/24h IV >12 years: Administer as in adults Cernevit <12 years: 2.5 mL/24h IV >12 years: Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Hydralazine and isoniazid may decrease effect of pyridoxine; pyridoxine may decrease effect of levodopa
Pregnancy	A - Fetal risk not revealed in controlled studies in humans
Precautions	Pregnancy category C if doses above RDA recommendations; caution in severe renal or liver failure; children may require additional vitamin A

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FOLLOW-UP

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Further Outpatient Care

- After the diagnosis is made and treatment is initiated, the primary care physician can follow up with the patient.

Deterrence/Prevention

- Pyridoxine (vitamin B_6) deficiency
  - Patients receiving isoniazid should receive pyridoxine 30 mg/d as prophylaxis.
  - Those receiving penicillamine should receive pyridoxine 100 mg/d.
  - Doses of more than 0.2 g/d have been associated with chronic sensory neuropathy.
  - The recommended daily allowance for men is 2 mg/d.
- Alpha-tocopherol (vitamin E)
  - In patients with cystic fibrosis, short-bowel syndrome, or deficiency of vitamin E transporter, monitor the serum a-tocopherol level.

- In those with cholestatic disease, monitor the ratio of serum a-tocopherol level to total serum lipid level.
- For those with abetalipoproteinemia, use the adipose tissue percentage or results of erythrocyte hydrogen peroxide assay. (Serum a-tocopherol measurements are inaccurate in this disorder.)

- Bariatric surgery
  - The chance of developing peripheral neuropathy is less in those who have surgery performed at the Mayo Clinic, do not have a jejunoileal bypass, take vitamin and calcium supplements, and attend nutritional clinics postoperatively.
  - Increased risk is associated with greater and faster weight loss; lower postsurgery BMI; lower serum albumin and transferrin; prolonged postoperative nausea, vomiting, diarrhea, and dumping; and postoperative complications requiring rehospitalization.

Prognosis

- An acute decrease in vitamin levels causes acute symptoms of vitamin deficiency but few morphologic changes. However, as the deficiency becomes chronic over months to years, such changes eventually take place.
  - In severe chronic deficiency states, response to pharmacologic treatment may be prolonged or nonexistent, as axonal degeneration can be halted but sometimes not reversed.
  - Improvement is always slow and, although peripheral nerves regenerate at a rate of 1 mm/d, full recovery cannot occur if the neuronal cell body or proximal neuron is damaged or if central pathways have been damaged.
- Thiamine (vitamin B_1) deficiency: Recovery is slow, often leaving residual muscular weakness and atrophy. In areas of endemic deficiency, the mortality rate from cardiac causes if untreated is 25-70%.
- Cyanocobalamin (vitamin B_{12}) deficiency: Rapid improvement occurs almost immediately after treatment is begun. Gradual improvement occurs over the next 4-6 months.
- Alcohol neuropathy: Slow incomplete recovery occurs in weeks to months.
- Vitamin E neuropathy: Recovery is incomplete.
- Pyridoxine (vitamin B_6) excess: Most patients improve with discontinuation; few cases resolve entirely.
- Malnutrition neuropathy: About 5% of patients have permanent and symptomatic neurologic damage because of extensive degeneration in the distal ends of posterior column fibers. Another 5% have deficiencies, as noted on physical examination.

Patient Education

- Dietary information on nutrition should be provided.
- Patients who use nutritional supplements should be warned that, although pyridoxine is water soluble and excreted in the urine, they still should not take too much.

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MULTIMEDIA

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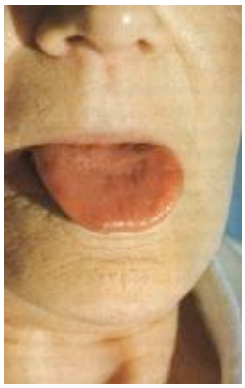
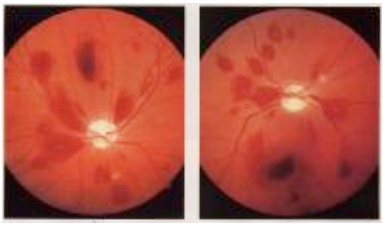
Media file 1: **Pernicious anemia. Characteristic lemon-yellow–tinged pallor with raw-beef tongue lacking filiform papillae. Used with permission from Forbes and Jackson.**



View Full Size Image

Media type: Photo

Media file 2: **Ischemic retinopathy caused by severe megaloblastic anemia.**



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Media type: Photo

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Nutritional Neuropathy excerpt

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