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Neurologic Presentations of Nutritional Deficiencies

Nutritional deficiency

Particularly important for optimal functioning of the nervous system are the **B-group** vitamins (vitamin B12, thiamine, niacin, and pyridoxine), **vitamin E**, **copper**, and folic **acid**. Not infrequently multiple nutritional deficiencies coexist

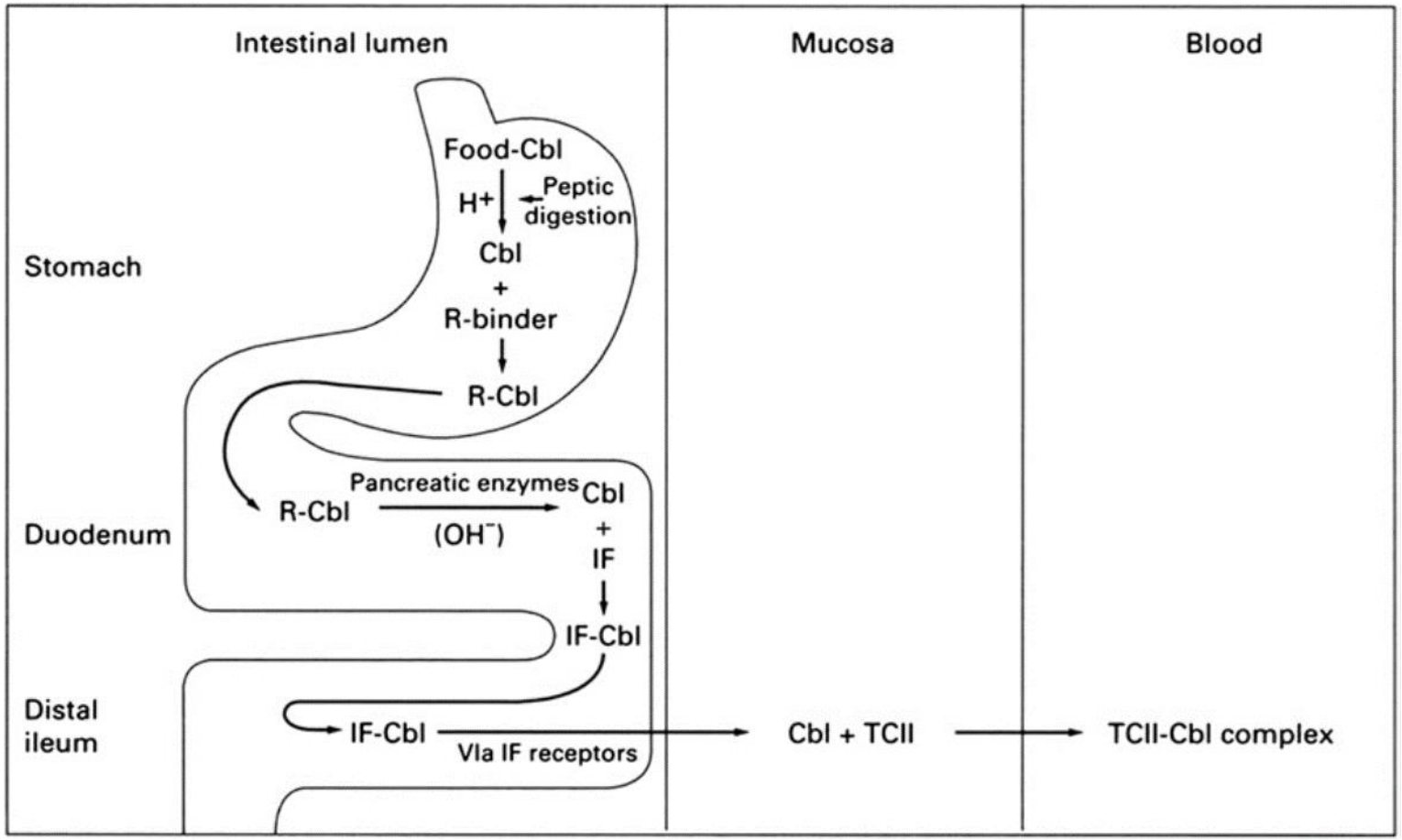
Neurologic Complications

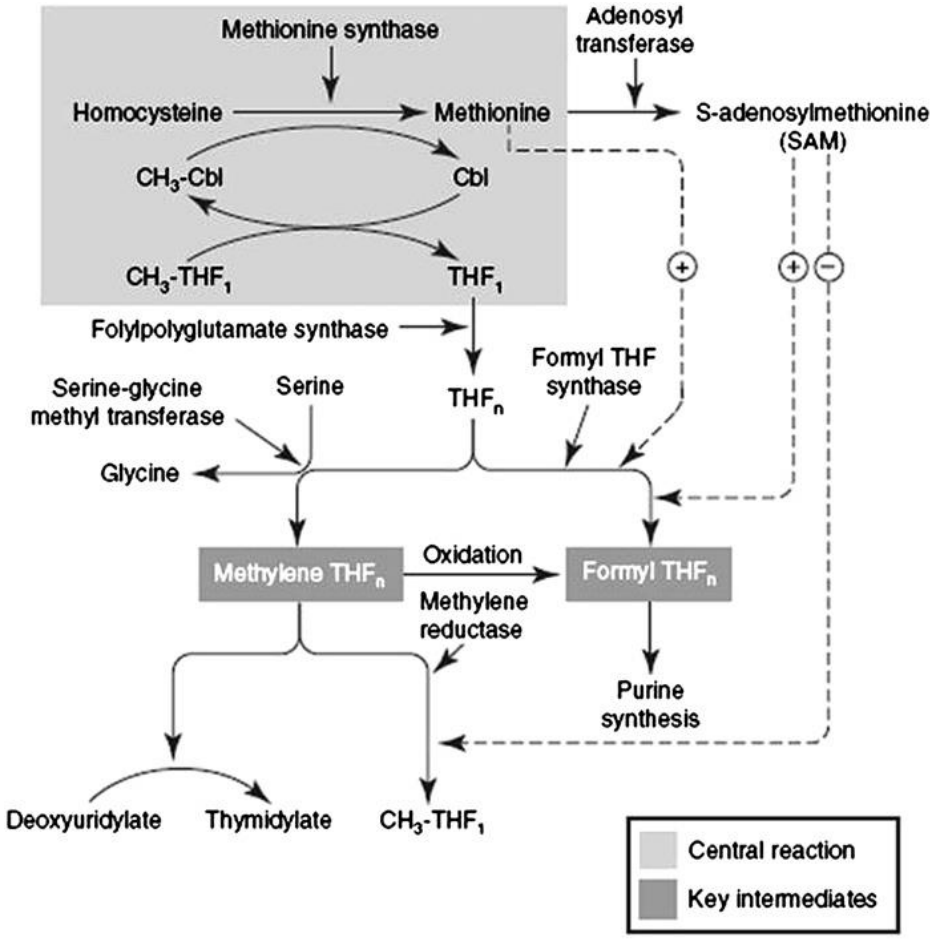
review discusses neurologic manifestations related to deficiency of key nutrients such as vitamin B12, folate, copper, vitamin E, thiamine, and others The second section addresses neurologic complications related to bariatric surgery. The third sections includes neurologic presentations caused by nutrient deficiencies in the setting of alcoholism

some recent review articles and book chapters for additional references.

Neurologic Presentations of Nutritional Deficiencies. Neurologic Clinics

NEUROLOGICMANIFESTATIONS RELATED TO DEFICIENCIES OF Vitamin B12/Foic





Cobalamin (Cbl); CH_3 = methyl group; THF_1 and THF_n = monoglutamated and polyglutamated forms of tetrahydrofolate

Causes of deficiency

- malabsorption related to intrinsic factor
- Cbl deficiency is commonly seen following gastric surgery
- Acid reduction therapy
- Other causes ; fish tapeworm, patients infected with HIV, Nitrous oxide (N2O, ‘‘laughing gas’’),

Clinical significance

- Myelopathy with or without an associated neuropathy
- cognitive impairment
- optic neuropathy (centrocecal scotomas)
- paresthesias without abnormal signs.

Table 1
Summary of sources, causes of deficiency, neurologic significance, laboratory tests, and treatment of deficiency states related to Cbl, folate, copper, vitamin E, thiamine, niacin, and pyridoxine

Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated with Deficiency	LaboratoryTests	Treatment	Additional Comments
Cobalamin	Meats, egg, milk, fortified cereals, legumes	Pernicious anemia, elderly (caused by atrophic gastritis and food-Cbl malabsorption), gastric surgery, acid reduction therapy, gastrointestinal disease, parasitic infestation by fish tapeworm, hereditary enzyme defects, N_2O toxicity, rarely strict vegetarianism, often unknown	Myelopathy or myeloneuropathy, peripheral neuropathy, neuropsychiatric manifestations, optic neuropathy, autonomic dysfunction	Serum Cbl, serum MMA, plasma total Hcy, hematologic tests (anemia, macrocytosis, neutrophil hypersegmentation), Schilling test, serum gastrin, intrinsic factor and parietal cell antibodies	IM B_{12} 1000 μg twice weekly for 2 weeks (or 100 μg twice weekly for 2 weeks), followed by weekly for 2 months and monthly thereafter or IM B_{12} 1000 μg daily for the first week, followed by weekly for the first month, then monthly thereafter; CyanoCbl is the form commonly used in United States, hydroxoCbl is the form preferred in parts of Europe; it requires less frequent injections and may be more allergenic	Even in the presence of severe malabsorption, 2–5 years may pass before cobalamin deficiency develops Disturbance in cobalamin metabolism in AIDS-associated myelopathy

Causes of folate deficiency

- Alcoholism pregnancy, lactation, and chronic hemolytic anemia.

- small bowel disorders associated with malabsorption such as tropical sprue, celiac disease, bacterial over- growth syndrome, giardiasis, and inflammatory bowel disease.

- Drugs such as aminopterin, **methotrexate**, **pyrimethamine**, **trimethoprim**, **anticonvulsants**, **antituberculosis drugs**, **sulfasalazine**, and **oral contraceptives**

Clinical significance

- may increase the risk of **cardiovascular disease**, **cerebrovascular disease**, peripheral vascular disease, venous thrombosis, cognitive impairment

- The myeloneuropathy or neuropathy or megaloblastic anemia seen in association with folate deficiency is indistinguishable from Cbl deficiency

Table 1
Summary of sources, causes of deficiency, neurologic significance, laboratory tests, and treatment of deficiency states related to Cbl, folate, copper, vitamin E, thiamine, niacin, and pyridoxine

Folate	In virtually all foods (spinach, yeast, peanuts, liver, beans such as kidney beans and lima beans, broccoli are particularly rich sources) (grains and cereals are fortified with folic acid)	Alcoholism, gastrointestinal disease, folate antagonists (eg, methotrexate, trimethoprim), errors of folate metabolism Folate deficiency generally coexists with other nutrient deficiencies	Neurologic manifestations are rare and indistinguishable from those caused by Cbl deficiency	Serum folate, RBC folate (more reliable indicator of tissue stores than serum folate), plasma total Hcy	Oral folate 1 mg 3 times a day followed by a maintenance dose of 1 mg a day; for acutely ill patients 1–5 mg/d (parenteral); supplementation with 0.4 mg/d in women in child bearing as for prophylaxis against neural tube defects	Clinically significant depletion of body folate stores may be seen in weeks-months Higher requirements in pregnancy, lactation, methotrexate toxicity Folate in foods have a bioavailability of less than 50%, folic acid supplements are in the monoglutamate form and have a bioavailability approaching 100% The reduced folates in food are labile and readily lost under certain cooking conditions such as boiling

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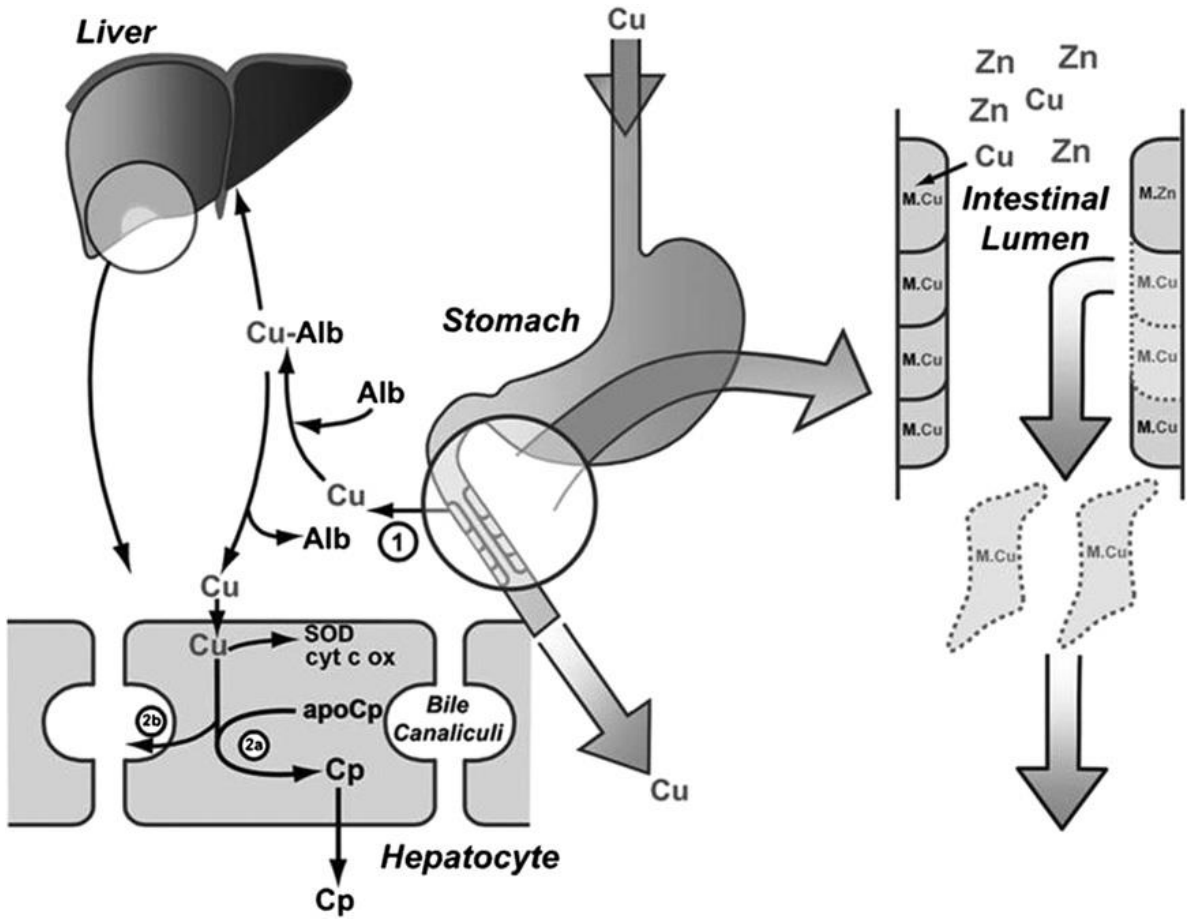
NEUROLOGICMANIFESTATIONS RELATED TO DEFICIENCIES OF Zinc-and Copper



Causes of deficiency

- deficiency include nephrotic syndrome, glomerulonephritis, and enteropathies associated with malabsorption such as celiac disease, cystic fibrosis, Crohn disease, sprue, bacterial overgrowth,

- The commonest identified cause of copper deficiency in patients with a copper deficiency myelopathy has been reported to be a prior history of gastric surgery.

- Parenteral zinc overloading during chronic hemodialysis has also been associated with copper deficiency myelopathy

Neurologic manifestations of acquired copper deficiency

- The most common manifestation is a myelopathy or myeloneuropathy that resembles the subacute combined degeneration seen with vitamin B_{12} deficiency.

- It presents with a spastic gait and prominent sensory ataxia. The sensory ataxia is primarily caused by dorsal column dysfunction.

- Clinical or Progressive, asymmetric weakness or electrodiagnostic evidence of denervation suggestive of lower motor neuron disease has also been reported.

- Copper and vitamin B_{12} deficiency may coexist. Continued neurologic deterioration in patients with a history of B_{12}-related myelopathy who have a normal B_{12} level while on replace ment therapy should be evaluated for copper deficiency.

neurologic manifestations of acquired copper deficiency

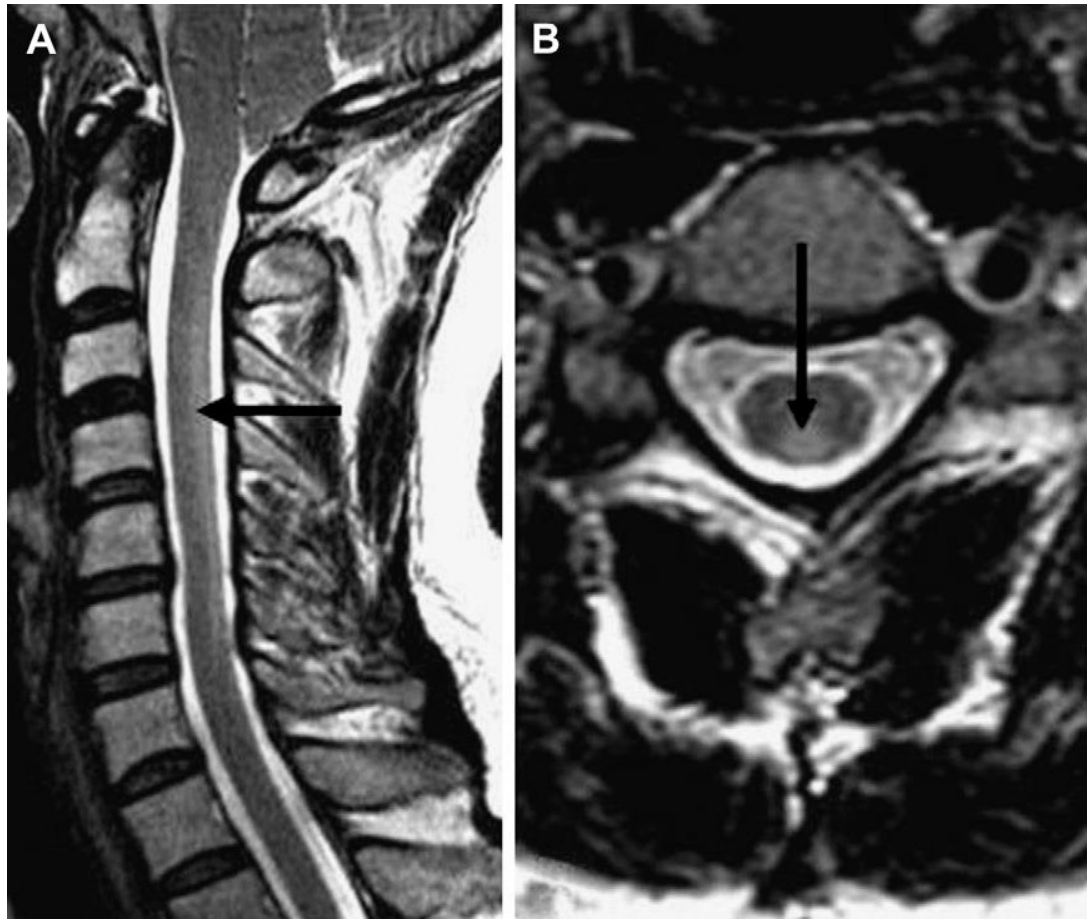
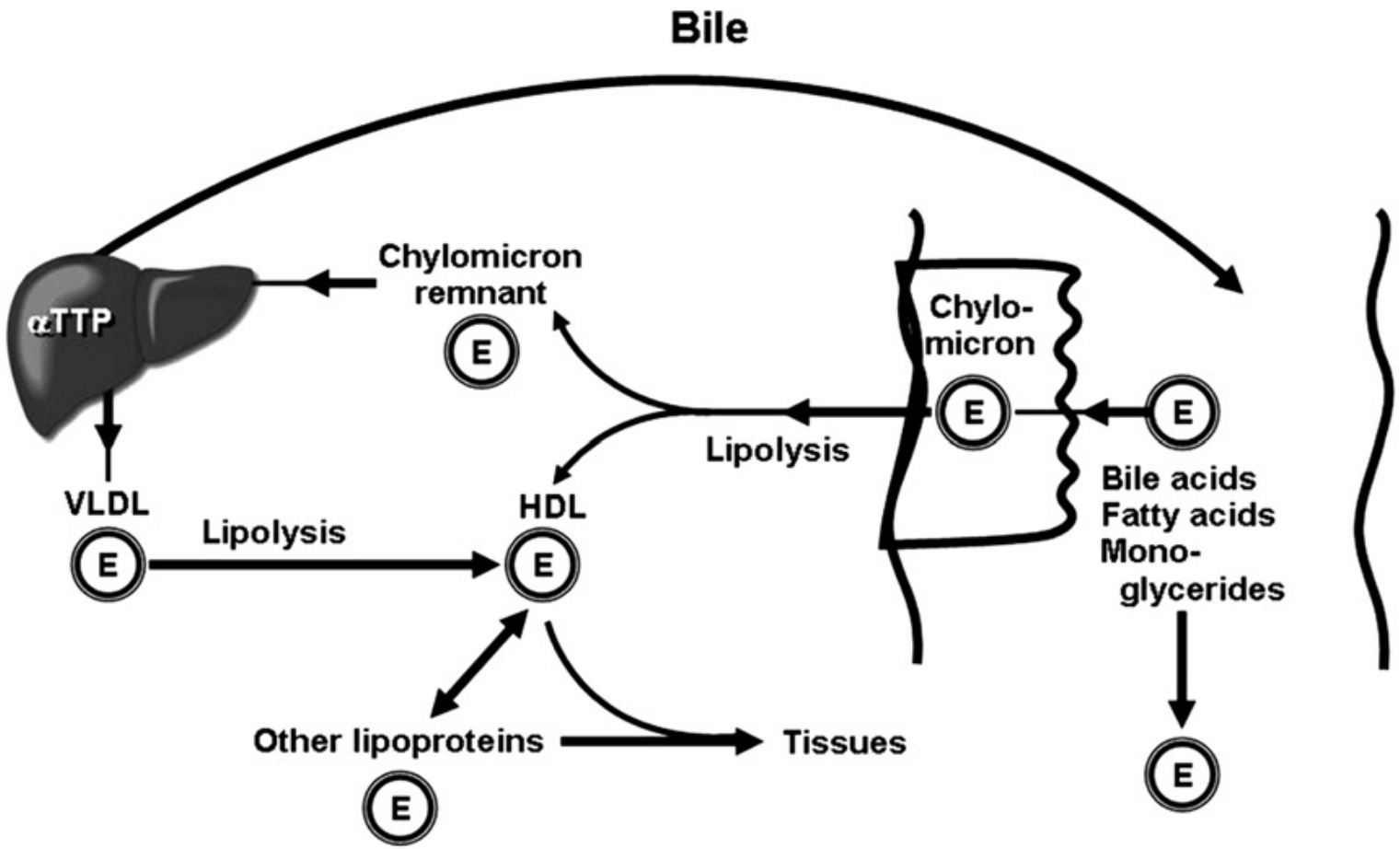


Table 1
(*continued*)

Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated with Deficiency	Laboratory Tests	Treatment	Additional Comments
Copper	Organ meats, seafood, nuts, mushroom, cocoa, chocolate, beans, whole grain products	Gastric surgery, zinc toxicity, gastrointestinal disease, total parenteral nutrition and enteral feeding, rarely acquired dietary deficiency, often unknown	Myelopathy or myeloneuropathy	Serum and urinary copper, serum ceruloplasmin, serum and urinary zinc, hematologic parameters (anemia, neutropenia, vacuolated myeloid precursors, ringed sideroblasts, iron-containing plasma cells)	Oral elemental copper: 8 mg/d for a week, 6 mg/d for the second week, 4 mg/d for the third week and 2 mg/d thereafter	Hyperzincemia of indeterminate cause may be present even in the absence of excess zinc ingestion Speculative if copper deficiency may have been responsible for subacute myelo-optic neuropathy (secondary to clioquinol)

Vitamin E


Bile
αTTP
Chylomicron remnant
E
Chylo-micron
E
E
Lipolysis
VLDL
E
Lipolysis
HDL
E
Bile acids
Fatty acids
Mono-glycerides
E
Other lipoproteins
E
Tissues

Causes of deficiency

- vitamin E deficiency is seen with chronic cholestasis and pancreatic insufficiency. celiac disease, Crohn disease, cystic fibrosis, biliary atresia, blind loop syndrome, bowel irradiation, extensive small bowel resection.

- Vitamin E supplementation in total parenteral nutrition may be inadequate to maintain vitamin E stores

Clinical significance

- The neurologic manifestations of vitamin E deficiency include a spinocerebellar syndrome with variable peripheral nerve involvement.

Table 4
Summary of disorders of vitamin E metabolism

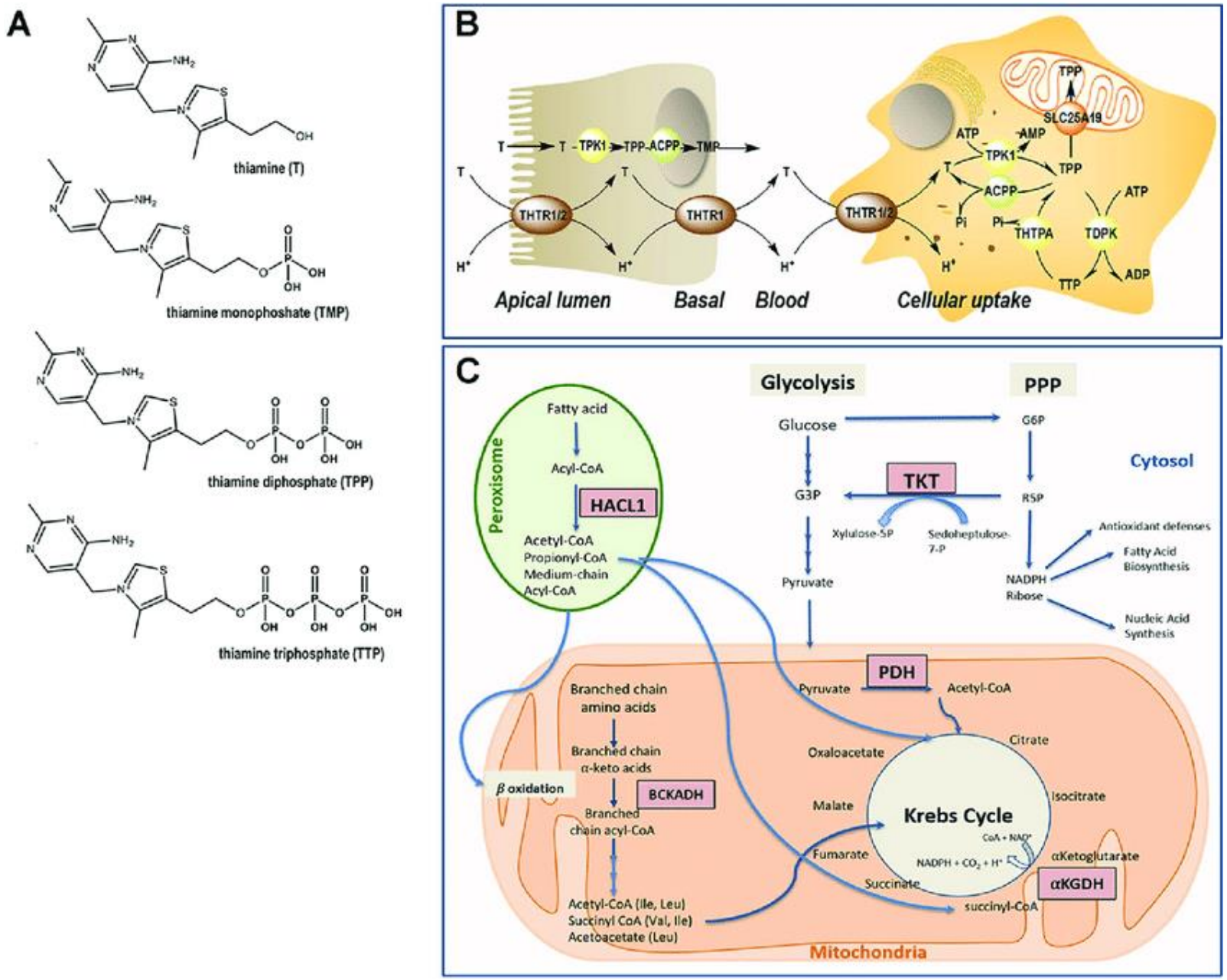
Disease	AVED	Homozygous Hypobetalipoproteinemia	Abetalipoproteinemia (Bassen-Kornzweig Disease)	Chylomicron Retention Disease
Source of defect	Mutations in α-TTP gene on chromosome 8q13 (AR)	Defect in apolipoprotein B gene (AD)	Genetic defect in microsomal triglyceride transfer protein (AR)	Chylomicron synthesis and secretion
Consequence of defect	Impaired incorporation of vitamin E into hepatic lipoproteins for tissue delivery	ApoB-containing lipoproteins secreted into the circulation turnover rapidly	Normal lipidation of apoB is prevented and secretion of apoB-containing lipoproteins is virtually nonexistent	Impaired assembly and secretion of chylomicrons with chylomicron retention in intestinal mucosa
Fat malabsorption	Absent	Present	Present	Present
Age of onset	Generally first decade, adult onset described	Early childhood	Early childhood	Early childhood
Other clinical features	Retinitis pigmentosa, skeletal deformities, cardiomyopathy	Retinitis pigmentosa, acanthocytosis, retarded growth, steatorrhea		Impacts growth and has gastrointestinal manifestations but acanthocytes are essentially absent, neuromuscular manifestations are less severe, and ocular manifestations are subclinical
Laboratory findings	Very low serum vitamin E (as low as 1/100th of normal)	Low serum vitamin E and other fat-soluble vitamins, low to nondetectable circulating lipoproteins (apoB, chylomicrons, VLDLs, or LDLs), serum cholesterol and triglycerides are markedly reduced (The ratio of free to esterified cholesterol in plasma is normal in hypolipoproteinemia and elevated in abetalipoproteinemia)		Hypocholesterolemia, normal fasting triglycerides, reduced plasma LDL apoprotein B, absence of chylomicrons after a fat test meal
Treatment	800–1200 mg/d of vitamin E (prompt normalization of plasma α-tocopherol concentration)	100–200 mg/kg of vitamin E	100–200 mg/kg of vitamin E	100–200 mg/kg of vitamin E

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; AVED, ataxia with vitamin E deficiency; LDL, low density lipoprotein; TTP, thiamine triphosphate; VLDL, very low density lipoprotein.

Adapted from Kumar N. Metabolic and toxic myelopathies. Cont Spin Cord Root Plexus Disord 2008;14:91–115; Kumar N. Neurogastroenterology. Cont Neurol Manifest Syst Dis 2008;14:13–52; with permission.

Table 1
(*continued*)

Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated with Deficiency	LaboratoryTests	Treatment	Additional Comments
Vitamin E	Vegetable oils (sunflower and olive), leafy vegetables, fruits, meats, nuts, cereals	Chronic cholestasis (particularly in children), pancreatic insufficiency, gastrointestinal disease, AVED, homozygous hypobetalipo-proteinemia, abetalipo-proteinemia, chylomicron retention disease	Spinocerebellar syndrome with peripheral neuropathy, ophthalmoplegia, pigmentary retinopathy	Serum vitamin E Ratio of serum α-tocopherol to sum of serum cholesterol and triglycerides	Vitamin E ranging from 200 mg/d to 200 mg/kg/d (oral, intramuscular); supplementation of bile slats in some patients	Vitamin E deficiency is virtually never the consequence of a dietary inadequacy Neurologic findings are rare in vitamin E-deficient adults with chronic cholestasis Vitamin E bioavailability is dependent on food fat



Neurological, Psychiatric, and Biochemical Aspects of Thiamine Deficiency in Children and Adults 10.3389/fpsyt.2019.00207

Box 1
Conditions or settings reported to be associated with thiamine deficiency

Increased requirements

Children, pregnancy, lactation, vigorous exercise

Critically ill

Hyperthyroidism

Malignancy, chemotherapy (eg, erbulozole, ifosfamide), bone marrow transplantation

Systemic infection, prolonged febrile illness

High glucose intake

Intravenous glucose administration

Refeeding after prolonged starvation

Data from Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6(5):442–5; Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. N Engl J Med 1985;312(16):1035–9.

Box 1
Conditions or settings reported to be associated with thiamine deficiency

Marginal nutritional status (decreased intake or decreased absorption or increased losses)

AIDS

Alcoholism

Anorexia nervosa, dieting, starvation, hunger strike, food refusal, dietary neglect in the elderly

Commercial dietary formula, slimming diets, food fads

Decreased absorption caused by excess use of antacids

Diet: polished rice, foods containing thiaminase or antithiamine compounds

Dietary supplements with herbal preparations

Gastrointestinal surgery (including bariatric surgery)

Inactivation of thiamine in food by excessive cooking of thiaminase-containing foods

Inadequate supplementation in parenteral or enteral nutrition

Thiamine loss related to loop diuretics therapy

Magnesium deficiency

Persistent vomiting (pancreatitis, migraine attacks, hyperemesis gravidarum) or diarrhea

Renal failure, hemodialysis, peritoneal dialysis

Severe gastrointestinal or liver or pancreatic disease

Tolazamide, high-dose nitroglycerine infusion (ethyl alcohol and propylene glycol on thiamine metabolism)

Clinical significance

- Beriberi
- Wernicke-Korsakoff syndrome

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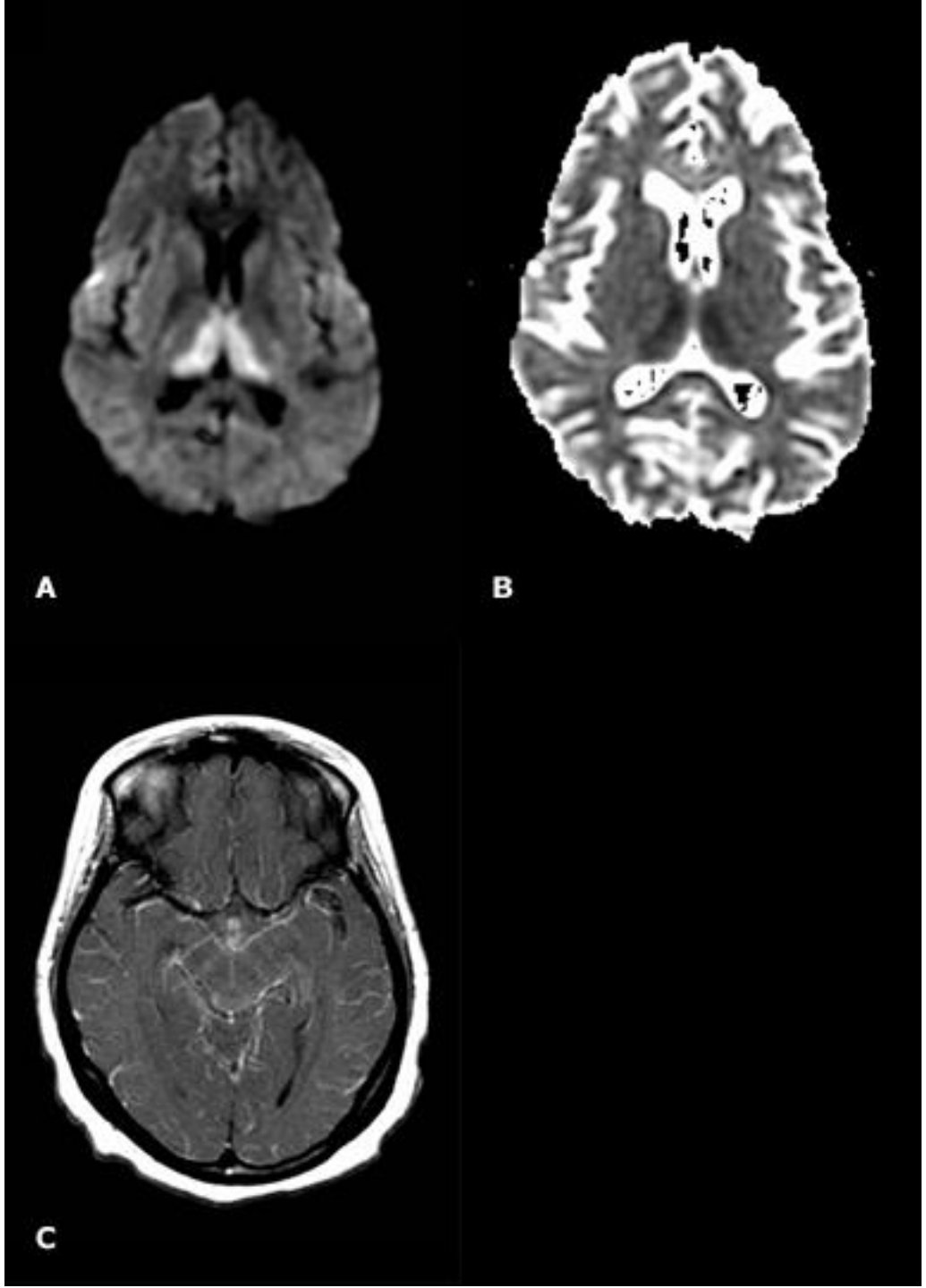
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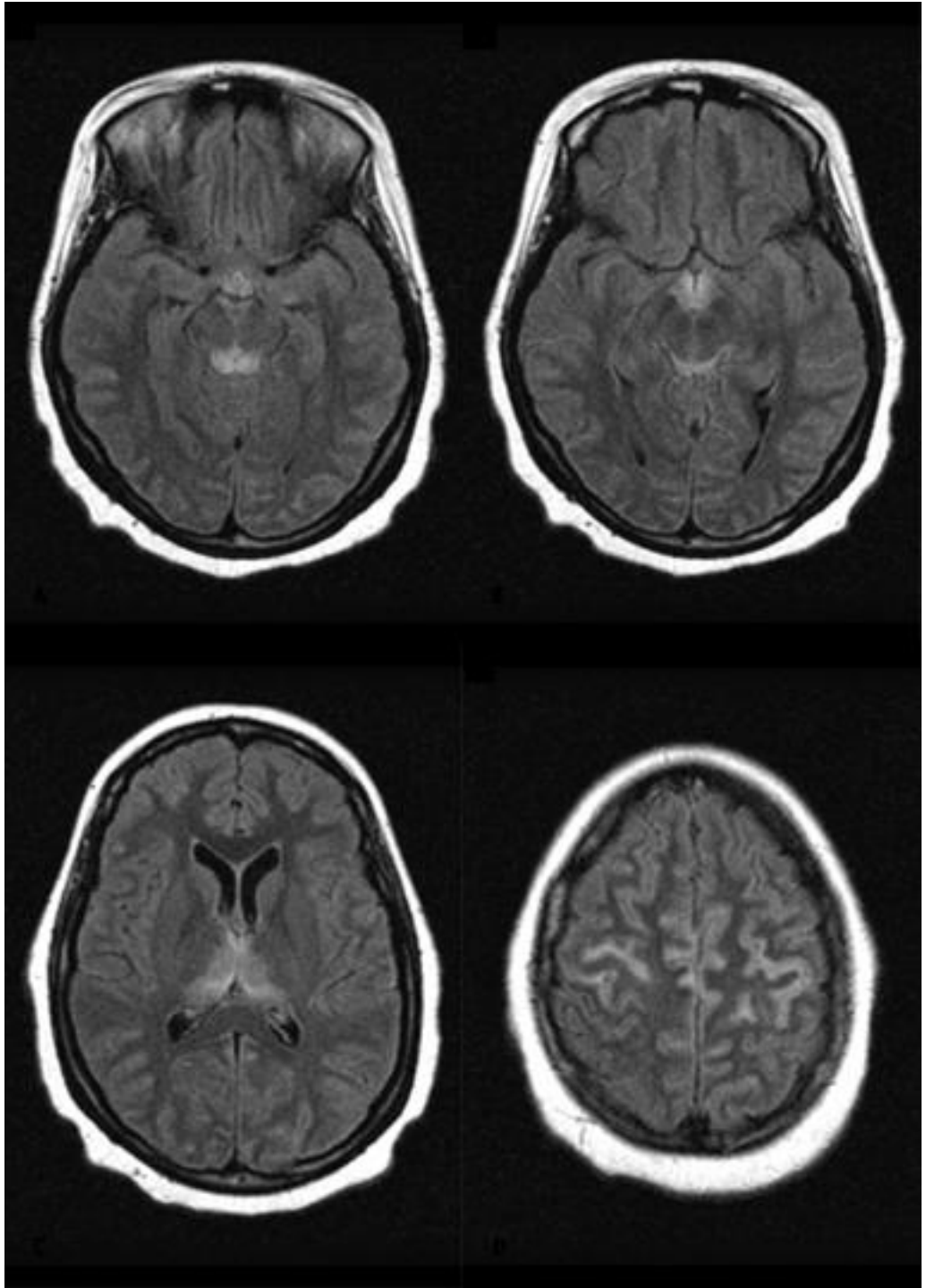

Table 1
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Nutrient	Sources	Major Causes of Deficiency	Neurologic Significance Associated with Deficiency	LaboratoryTests	Treatment	Additional Comments
Thiamin	Enriched, fortified, or whole grain products, organ meats	Recurrent vomiting, gastric surgery, alcoholism, dieting, increased demand with marginal nutritional status	Beriberi (dry, wet, infantile), WE, KS	Urinary thiamin, serum thiamin, erythrocyte transketolase activation assay, RBC thiamin diphosphate	50–300 mg/d of thiamine (intravenous, intramuscular, oral); higher doses may be required in WE; infantile beriberi: 5–20 mg of parenteral thiamine	At risk patients should receive parenteral thiamine before administration of glucose or parenteral nutrition
Niacin	Meat, fish, poultry, enriched bread, fortified cereals	Corn as primary carbohydrate source, alcoholism, malabsorption, carcinoid and Hartnup syndrome	Encephalopathy (peripheral neuropathy)	Urinary excretion of methylated niacin metabolites	25–50 mg of nicotinic acid (intramuscular, oral)	
Pyridoxine	Meat, fish, eggs, soybeans, nuts, dairy products	B_6 antagonists (INH, hydralazine, penicillamine), alcoholism, gastrointestinal disease	Infantile seizures, peripheral neuropathy (pure sensory neuropathy with toxicity)	Plasma pyridoxal phosphate	50–100 mg of pyridoxine daily (oral); pyridoxine supplementation in patients on isoniazid	

Abbreviations: AVED, ataxia with vitamin E deficiency; Cbl, cobalamin; Hcy, homocysteine; IM, intramuscular; INH, isoniazid; KS, Korsakoff syndrome; MMA, methylmalonic acid; RBC, red blood cell; WE, Wernicke encephalopathy.

From Kumar N. Nutritional neuropathies. Neurol Clin 2007; 25(1): 209-55

NEUROLOGIC COMPLICATIONS RELATED TO BARIATRIC SURGERY

- B_{12} deficiency is the most common nutritional deficiency
- Thiamine deficiency has been reported as early as 2 weeks and as late as 20 years
- The most commonly identified mineral deficiency following bariatric surgery is iron and may be seen in nearly 50% of patients.

Alcoholic Neuropathy

slowly progressive, distally predominant, painful, symmetric, sensorimotor, axonal neuropathy with preferential small fiber involvement and autonomic dysfunction.

segmental demyelination and remyelination resulting from widening of consecutive nodes of Ranvier may be more frequent in alcoholic neuropathy.

Some patients may have a subacute presentation that mimics Guillain-Barre syndrome.

Alcoholic Cerebellar Degeneration

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Truncal ataxia with a wide based gait and difficulty with tandem walking. Limb ataxia, if present, is milder and more evident in the lower limbs. accompanying polyneuropathy

Vermal atrophy in alcoholic cerebellar degeneration may relate to thiamine deficiency

Tobacco-alcohol Amblyopia

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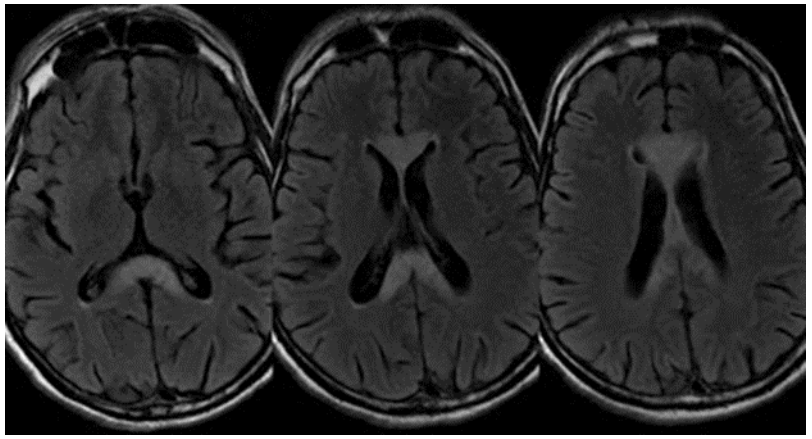
Bilateral, progressive, painless visual loss in severe alcoholics caused by damage to the papillomacular bundle central or cecocentral scotomas and peripapillary hemorrhages.

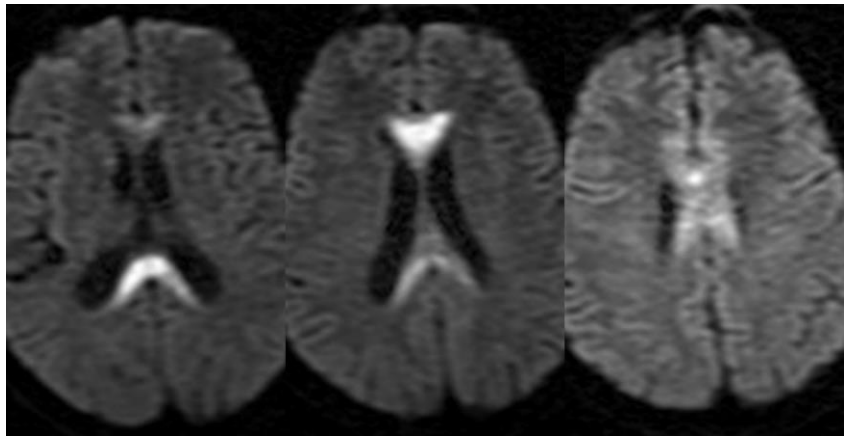
The syndrome is similar to the amblyopia seen in prisoners of war and malnourished individuals. Partial visual recovery may result with an adequate diet and B vitamins, despite continued use of alcohol and tobacco.

Marchiafava-Bignami

- personality change, psychomotor slowing. dysarthria, quadriparesis, incontinence, seizures, symptoms of interhemispheric disconnection, and rarely coma.

- The central part of the body of the corpus callosum is preferentially involved by acute demyelination and necrosis.





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