Vitamin and Minerals and Neurologic Disease

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Disclosures

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Objective

- Discuss the association of trace mineral deficiencies and vitamin deficiencies (and excess) with neuropathy and myeloneuropathy and other peripheral neurologic syndromes
Outline of Presentation

- List minerals relevant to neuropathy or myeloneuropathy
- Proceed through each mineral and its associated clinical syndrome
- List vitamins relevant to neuropathy or myeloneuropathy
- Proceed through each vitamin and its associated clinical syndrome
Minerals

- Naturally occurring nonorganic homogeneous substances
- Elements
- Required for optimal metabolic and structural processes
- Both cations and anions
- Essential trace minerals: must be supplied in the diet
- Some have recommended daily allowances (RDA)
Macrominerals

- Sodium
- Potassium
- Calcium
- Magnesium
- Phosphorus
- Sulfur
Macrominerals

- Sodium
- Potassium
- Calcium
- Magnesium
- Phosphorus
- Sulfur
Trace Minerals

- Chromium
- Cobalt
- Copper
- Iodine
- Iron
- Manganese
- Molybdenum
- Selenium
- Zinc
Trace Minerals

- Chromium
- Cobalt
- Copper
- Iodine
- Iron
- Manganese
- Molybdenum
- Selenium
- Zinc
Generalized dose-response curve for an essential nutrient

Howd and Fan, 2007
Copper

- Essential trace element
- Human body contains approximately 100 mg Cu
- Cofactor of many redox enzymes
- Ceruloplasmin most abundant of the cuproenzymes
- Involved in antioxidant defense, neuropeptide and blood cell synthesis, and immune function\(^1\)

\(^1\) Bost, J Trace Elements 2016
Copper Deficiency

- Causes myelopathy indistinguishable from B12 deficiency
- Posterior column signs, spasticity, myeloneuropathy
- Hematologic: anemia, pancytopenia
- Optic neuropathy
- Malabsorption, malnutrition, parenteral feeds
- Zinc ingestion interferes with copper absorption
- Treatment: copper replacement, removal of zinc
Copper Deficiency—Causes

- Malabsorption, malnutrition, parenteral feeds
- Zinc ingestion interferes with copper absorption
- Treatment: copper replacement, removal of zinc (eg, denture cream, zinc supplements)
Case

- 53 y/o woman with 4 months of progressive distal paresthesias
- 3 months prior: normocytic anemia, leukopenia
- Medication: zinc supplements
- Examination:
  - Increased tone in LEs, hyperactive KJs; decreased vibration & proprioception; sensory ataxic gait; MRI cord normal
- EMG
  - Length-dependent primarily axonal motor and sensory PN in Les
- Routine labs: WBC 2.6, MCV 112.5

1 Rowin, Lewis JNNP 2005
Case

- Cu 7 mg/dl (nl > 70); Zn 2.28 mg/ml (nl < 1.10)
- Tx: Copper replacement, discontinuation of zinc
- Hematologic parameters improved at 3 months
- Gait improved at 6 months
- F/U NCS 6 months later: normalization of sural response

1 Rowin, Lewis JNNP 2005
Copper Deficiency Neuropathy

- Mayo study\(^1\): 34/98 patients with copper deficiency had peripheral neuropathy
- Numbness and gait impairment in most; vibratory loss in all
- Decreased ankle reflexes in 41%

\(^1\) Taylor et al, JNNP 2017
Copper Deficiency Neuropathy\textsuperscript{1}

- EMG: large > small fiber sensory predominant, length dependent axonal neuropathy; evidence for autonomic dysfunction
- Bx: Neurogenic: axonal degeneration, empty nerve strands, decreased density of large and small myelinated and unmyelinated fibers
- 38\% of patients had no evidence of myelopathy: neuropathy may be large contributor to sensory ataxia.

\textsuperscript{1} Taylor et al, JNNP 2017
Chromium

- Essential trace element
- Required for sugar and fat metabolism
Chromium Deficiency

- Associated with glucose intolerance requiring insulin
- Absorption impaired by zinc
- Case: Neuropathy in 40 y/o woman on TPN with low chromium; neuropathy and glucose intolerance improved with replacement\(^1\)
- Case: Neuropathy and glucose intolerance in patient on TPN with low chromium (also on metronidazole); improved only after chromium replacement\(^2\)
- Chromium deficiency may be a treatable cause of neuropathy

\(^1\) Jeejeebhoy et al, Am J Clin Nutr 1977
\(^2\) Verhage et al, JPEN 1996
Phosphorus Deficiency

- Associated with acute sensorimotor polyneuropathy
- Seen in IV hyperalimentation without inorganic phosphate
- Distal paresthesias and weakness, areflexia
- Resembles GBS or critical illness neuromyopathy
Phosphorus Deficiency

- Neurophysiology: Absent F-waves\(^1\), or slow NCVs/prolonged distal latencies\(^2\)
- Clinical/NCS improve with repletion of inorganic phosphate\(^{1,2}\)
- Consistent with functional impairment

\(^1\)Igochi, JNNP 2006
\(^2\)Siddiqui, Muscle Nerve 1998
Selenium

- Essential trace element
- Inorganic form: sodium selenite
- Organified in wheat as an amino acid containing sulfur (Se-methylselenocysteine); incorporated in humans as the amino acid L-Selenocysteine
- Component of 25 selenoproteins in humans; antioxidant enzymes, including glutathione peroxidases, scavengers of hydroperoxidases
- Selenocysteine resides in active site of glutathione peroxidase
A  Sodium Selenite

\[ \text{Na}_2\text{SeO}_3 \]

B  L-Selenocysteine

\[ \text{HSeCH}_2\text{CONH}_2\text{OH} \]
White Muscle Disease

- In animals
- Due to fibrosis and calcium deposition
- In skeletal & cardiac muscle
- Found in 1958 to be prevented by selenium in diet
Keshan Disease

- 1935: Rapidly progressive *cardiomyopathy* in Keshan, China
- Initially thought to be infectious
- Reappeared in 1960s in Sichuan and Yunnan provinces
- 80% case fatality; most vulnerable: children age 2-7 and women of childbearing age
- Pathology: Myocardial pallor due to fibrosis and necrosis, myocytolysis, similar to white muscle disease
Keshan Disease

- Studies from 1960s-1980s:
  - Low selenium levels in soil and blood and local foods found
  - Correlated with distribution of Keshan disease cardiomyopathy
- Keshan disease prevented since 1990s by oral selenium supplementation
Sequence of Mechanisms Leading from Selenium Deficiency to Cardiomyopathy
Human White Muscle Disease

- 28 y/o woman with anorexia nervosa, started TPN\(^1\)
- One month later: proximal muscle pain and weakness, difficulty walking and standing
- CK 5638 IU/L; selenium 13 mcg/L (nl 107-171); glutathione peroxidase 145 IU/L (nl 280-450)
- Myopathic EMG; normal sensory and motor NCS
- Symptoms improved in 2 months with change to oral diet
- Other reported cases: 18/19 improved, median 4 weeks\(^2\)

\(^1\) Ishihara, JNNP 1999
\(^2\) Chariot, Muscle & Nerve 2003
A. H&E stain showing atrophic changes and intrafibral vacuoles; B. ATPase stain showing Type II fiber predominance and many vacuoles.
Molybdenum

- Essential cofactor in xanthine oxidase dehydrogenase and sulfite oxidase
- Enzymes that protect CNS from dietary purine (and sulfite) loading

1 Bourke, Front Neurol 2016
Molybdenum

- Motor neuron diseases in sheep related to Mo deficiency:
  - Xanthosine motor neuron syndrome
    - Progressive and irreversible asymmetric muscle weakness one pelvic limb, and later in the corresponding limb, with atrophy
    - Due to xanthosine (purine) ingestion in setting of Mo deficiency
  - Inosine motor neuron syndrome
    - Progressive and irreversible bulbar and respiratory muscle weakness
    - Due to inosine (purine) ingestion during Mo deficiency
- Possible model for human motor neuron disease?

1 Bourke, Front Neurol 2016
Vitamins and Neuropathy

- Vitamin B12 (cobalamin) deficiency
- Vitamin B1 (thiamine) deficiency
- Vitamin B6 (pyridoxine) deficiency and excess
Vitamin B12 (Cobalamin)

- Cofactor for two important enzymes
  - Methionine synthase
  - L-methyl-malonyl-coenzyme A mutase
- Cellular energy creation
- DNA/RNA synthesis/repair
- Creation of hormones, proteins and lipids
Vitamin B12 (Cobalamin) Deficiency
Vitamin B12 Absorption Pathway

- Cobalamin in stomach → bound to haptocorrin
- Travels to duodenum, enzymes degrade haptocorrin → free cobalamin then binds to intrinsic factor
- Travels to ileum → Intrinsic factor-B12 complex binds to receptor in ileum → internalized in cells of small bowel
- In circulation, cobalamin heavily protein bound (80% haptocorrin (not usable), 20% transcobalamin II)
- Note B12 levels measure total B12

B12 (Cobalamin) Food Sources

- Found in most animal derived foods, B12-fortified foods
- NIH dietary recommendations: 2.4 mcg daily allowance >14 years of age
- 2.6 mcg during pregnancy and 2.8 mcg during lactation

<table>
<thead>
<tr>
<th>Food</th>
<th>Micrograms (mcg) per serving</th>
<th>Percent DV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clams, cooked, 3 ounces</td>
<td>84.1</td>
<td>1,402</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3 ounces</td>
<td>70.7</td>
<td>1,178</td>
</tr>
<tr>
<td>Breakfast cereals, fortified with 100% of the DV for vitamin B12, 1 serving</td>
<td>6.0</td>
<td>100</td>
</tr>
<tr>
<td>Trout, rainbow, wild, cooked, 3 ounces</td>
<td>5.4</td>
<td>90</td>
</tr>
<tr>
<td>Salmon, sockeye, cooked, 3 ounces</td>
<td>4.8</td>
<td>80</td>
</tr>
<tr>
<td>Trout, rainbow, farmed, cooked, 3 ounces</td>
<td>3.5</td>
<td>58</td>
</tr>
<tr>
<td>Tuna fish, light, canned in water, 3 ounces</td>
<td>2.5</td>
<td>42</td>
</tr>
<tr>
<td>Cheeseburger, double patty and bun, 1 sandwich</td>
<td>2.1</td>
<td>35</td>
</tr>
<tr>
<td>Haddock, cooked, 3 ounces</td>
<td>1.8</td>
<td>30</td>
</tr>
<tr>
<td>Breakfast cereals, fortified with 25% of the DV for vitamin B12, 1 serving</td>
<td>1.5</td>
<td>25</td>
</tr>
<tr>
<td>Beef, top sirloin, broiled, 3 ounces</td>
<td>1.4</td>
<td>23</td>
</tr>
<tr>
<td>Milk, low-fat, 1 cup</td>
<td>1.2</td>
<td>18</td>
</tr>
<tr>
<td>Yogurt, fruit, low-fat, 8 ounces</td>
<td>1.1</td>
<td>18</td>
</tr>
<tr>
<td>Cheese, Swiss, 1 ounce</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Beef taco, 1 soft taco</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Ham, cured, roasted, 3 ounces</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>Egg, whole, hard boiled, 1 large</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>Chicken, breast meat, roasted, 3 ounces</td>
<td>0.3</td>
<td>5</td>
</tr>
</tbody>
</table>

Table borrowed from: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/
Vitamin B12 Deficiency—Symptoms and Signs

- Peripheral nervous system
  - large fiber sensory/sensorimotor neuropathy, usually length dependent
  - small fiber neuropathy
  - autonomic dysfunction
  - rarely, sensory neuronopathy

- Central nervous system
  - subacute combined degeneration of spinal cord (posterior columns, lateral corticospinal tracts)
  - cognitive and mood changes
  - optic neuropathy: centrocecal scotoma
Vitamin B12 Deficiency—Symptoms and Signs

- Hematologic: megaloblastic anemia
- Glossitis
- Infertility
- Hyperpigmentation
Vitamin B12 (Cobalamin) Deficiency: Neuropathologic Changes

- Peripheral nerves
  - Loss of large myelinated fibers
  - axonal degeneration
  - secondary segmental demyelination

- Spinal cord
  - myelin sheath swelling, lamellae separation
  - intramyelinic vacuoles, similar to HIV vacuolar myelopathy

- Mechanism of pathology - unclear
  - ?DNA synthesis impairment
  - decreased methylation of myelin phospholipids
  - aberrant myelination due to impaired fatty acid synthesis
Vitamin B12 (Cobalamin) Deficiency: Electrophysiologic Changes

- Early: normal
- Later:
  - sensory nerve conduction velocity slowing
  - reduced amplitude sensory nerve action potentials
Vitamin B12 (Cobalamin) Deficiency: Etiology

- Severe or mild malabsorption
  - Pernicious anemia (loss of parietal cells, intrinsic factor)
  - Gastric bypass, bariatric surgery, gastrectomy, inflammatory bowel
  - Mild: atrophic gastritis with achlorhydria, bacterial overgrowth, H. pylori, Diphyllobothrium latum
  - Drug related: metformin, H2 blockers, PPIs

- Dietary deficiency
  - Vegetarian, vegan

- Genetic mutations
  - Methylmalonic-CoA mutase genetic mutation
Nitrous Oxide and B12 Deficiency

- Nitrous oxide inactivates the cobalt core of B12
- Recreational nitrous oxide use
- Anesthesia-related (nitrous oxide anesthesia with underlying B12 deficiency)

Vitamin B12 Deficiency: Diagnosis

- Extremely low (<100 pg/mL or <73.8 pmol/L) is usually symptomatic
- False negatives are common (highly protein bound) - up to 50% of tests
  - Low normal should not be diagnostic cutoff if suspicion is high
  - Aim for 400-500 pg/mL B12 levels
- Elevated methylmalonic acid and homocysteine levels are supportive of low B12
Vitamin B12 Deficiency: Treatment

- Oral sublingual, parenterally (usually IM), or intranasally
  - Oral: cyanocobalamin, methylcobalamin, hydroxycobalamin
    • Studies show no significant difference in bioavailability or absorption
    • Watch use of cyanocobalamin with renal failure
  - Sublingual
- IM dosing favored for severe, acute treatment
  - 1000 mcg IM q 3-7 days x1 month, then monthly
- High oral dosing may be as effective as IM administration
  - 2000 mcg daily initially, with 1000 mcg daily, then weekly
  - As effective as IM administration in obtaining short term responses
- Folate?
Vitamin B1 (Thiamine)

- Thiamine catalyzes decarboxylation of alpha-ketoacids to coenzyme A moieties in mitochondria
  - Important for ATP synthesis
- Thiamine plays role in formation of myelin
- Thiamine may also affect neuronal conduction by altering membrane sodium channel function
Vitamin B1 (Thiamine)—Food Sources

- Whole grains, meat (pork), fish, fortified grains
  - Thiamine stores are low (half life 10-14 days), need continuous sources
  - NIH recommends 1.2 mg daily for men, 1.1 mg daily for women >19 years
  - 1.4 mg daily allowance with pregnancy and lactation
- Heating food reduces thiamine content
- Thiamine absorbed in the small intestine (active and passive absorption)
Vitamin B1 (Thiamine) Deficiency—Symptoms

- Peripheral neuropathy (dry beriberi)
  - numbness, tingling, burning
  - stocking distribution sensory loss to all modalities, diminished reflexes
  - prominent component of pain
  - mild distal weakness or autonomic dysfunction

- Cardiac (wet beriberi)
  - Congestive heart failure, lower extremity edema, neuropathy

- Central nervous system
  - Wernicke’s encephalopathy: ophthalmoparesis, ataxia, confusion
  - Korsakoff’s syndrome
  - 80% have signs of peripheral neuropathy
Vitamin B1 (Thiamine) Deficiency: Peripheral Neuropathology

- Sural bx: Loss of primarily large myelinated axons
- Axonal degeneration and secondary demyelination of posterior columns
- Chromatolysis of anterior horn cells and dorsal root ganglia cells
Vitamin B1 Deficiency—Neurophysiology

- Reduced or absent sensory nerve action potentials amplitudes
- Relatively preserved distal sensory latencies and nerve conduction velocities
- Motor nerve action potentials: normal or slightly reduced amplitude
Vitamin B1 Deficiency—Etiology

- ETOH abuse
  - reduced intake/absorption
  - lower thiamine stores in liver
  - ETOH related thiamine phosphorylation
- Age
  - lower intake, low absorption, multiple medications
- Bariatric surgery
- HIV/AIDS
  - malnutrition due to catabolic state
- Hyperemesis
  - Pregnancy, chemotherapy
- Diabetes
Vitamin B1 Deficiency—Diagnosis

- Generally a clinical diagnosis
- Blood and urine tests are slow to result and unreliable
- Erythrocyte transketolase activity may be more accurate
Vitamin B1 Deficiency—Treatment

- No clear treatment guidelines available
- Earlier guidelines recommend 100 mg/day IV or IM with prolonged oral supplementation thereafter
- More recent suggestion of higher doses - 250-500 mg TID x 3 days, 100 mg po daily thereafter
- Thiamine has few adverse side effects (rare anaphylaxis)
- Benefits >>> risks
Vitamin B6 (Pyridoxine)

- Converted to pyridoxal 5’-phosphate in body (active form)
- B6 absorbed passively in jejunum and ileum
- Numerous important biochemical reactions for metabolism, synthesis of neurotransmitters, histamine, and hemoglobin synthesis and gene expression
- B6 food sources: widely distributed, found in meats, grains, vegetables, legumes, and bananas
Vitamin B6 (Pyridoxine) Deficiency

- Symptoms:
- Sensory > motor polyneuropathy
- Homocystinemia, increasing risk of vascular thrombosis
- Severe deficiency can cause seizures
- Electrophysiology: axonal sensorimotor polyneuropathy
Vitamin B6 Deficiency—Etiology and Tx

- **Causes of B6 Deficiency**
  - Most associated with treatment with isoniazid (increased excretion) and hydralazine (forms pyridoxal-hydralazine complex)
  - Chronic alcoholism, chronic peritoneal dialysis
  - Decreased levels found in Type 1 Diabetics, HIV, liver disease

- **Treatment**
  - In cases of malnutrition, 50 mg daily po for several weeks, followed by 2 mg daily
  - Should remain on 50 mg daily of B6 for duration of INH treatment
  - Watch for toxicity
Vitamin B6 (Pyridoxine) Toxicity

- Original description: seven adults with severe ataxia after megadoses of vitamin B6 use
- 2-6 grams/d
- Most severely disabled
- Sensory ataxia; no weakness
- Areflexia

*Schaumburg et al NEJM 1983*
Signs and Symptoms of Pyridoxine Toxicity

- Unsteady gait, numb feet
- Numbness and clumsiness of hands
- Later: perioral numbness
- Stocking-glove sensory loss to all modalities on exam
- Profound loss of vibration and position sense
- Absent or diminished reflexes
- Absent sensory nerve action potentials on NCSs
Table 1. Features of Seven Cases of Pyridoxine Abuse.

<table>
<thead>
<tr>
<th>CASE No.</th>
<th>AGE/Sex</th>
<th>REASON FOR TAKING B&lt;sub&gt;6&lt;/sub&gt;</th>
<th>MAXIMUM DAILY DOSE</th>
<th>DURATION OF CONSUMPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36/F</td>
<td>Health magazine advocated it for menstrual edema</td>
<td>2 g</td>
<td>4 mo</td>
</tr>
<tr>
<td>2</td>
<td>25/M</td>
<td>Self-imposed dietary supplement</td>
<td>3 g</td>
<td>4 mo</td>
</tr>
<tr>
<td>3</td>
<td>35/F</td>
<td>Self-imposed dietary supplement</td>
<td>2 g</td>
<td>40 mo</td>
</tr>
<tr>
<td>4</td>
<td>34/F</td>
<td>Gynecologist prescribed it for edema</td>
<td>2 g</td>
<td>34 mo</td>
</tr>
<tr>
<td>5</td>
<td>20/M</td>
<td>Orthomolecular psychiatrist prescribed it</td>
<td>6 g</td>
<td>3 mo</td>
</tr>
<tr>
<td>6</td>
<td>27/F</td>
<td>Self-imposed treatment for edema</td>
<td>5 g</td>
<td>2 mo</td>
</tr>
<tr>
<td>7</td>
<td>43/F</td>
<td>Gynecologist prescribed it</td>
<td>4 g</td>
<td>10 mo</td>
</tr>
</tbody>
</table>
Pyridoxine toxicity: Pathophysiology

- A sensory neuronopathy
- Possibly related to selected vulnerability of dorsal root ganglia to toxins
- ? Due to absence of blood/nerve barrier
Summary

- Neuropathy and myeloneuropathy may occur due to deficiencies of some essential minerals
- Myopathy may occur from selenium deficiency
- Neuropathy and myeloneuropathy may occur due to deficiencies of certain vitamins; dorsal root ganglionopathy from pyridoxine excess
- Deficiencies typically occur in setting of total parenteral nutrition; may occur due to other dietary factors, malabsorption
- Rare, but preventable, and possibly reversible, causes of neuromuscular and myeloneuropathy syndromes