

# **PERNICIOUS ANEMIA (B12 DEFICIENCY)**

## **Background**

### **1. Definition**

- Anemia due to lack of intrinsic factor in gastric secretions, which leads to impaired vitamin B12 absorption

### **2. General information**

- Intrinsic factor binds B12 → absorption of B12 in intestine
  - B12 cannot be absorbed unless bound to intrinsic factor
- Other causes of vitamin B12 deficiency exist
  - Inadequate dietary intake, gastrectomy, abnormal intrinsic factor function, bacterial overgrowth, ileal dysfunction
- Pernicious anemia is classically defined as above

## **Pathophysiology**

### **1. Pathology**

- Gastric parietal cells fail to make/secrete intrinsic factor
  - Thought to be due to an autoimmune disorder with genetic predisposition
  - Associated with HLA A2, A3, B7, and type A blood
  - Antiparietal cell antibodies (90% of pts.) as well as intrinsic-factor antibodies (50-75% of pts.) are present
    - Antibodies are postulated to lead to severe gastric atrophy and achlorhydria (lack of secretion of hydrochloric acid) (Gastroenterology 1989 Jun;96(6):1434)

### **2. Incidence/prevalence**

- Occurs most frequently in individuals of European origin
  - 10-20 cases per 100,000 people per year
    - Incidence of subclinical pernicious anemia appears to be higher: 1.9% of survey population had unrecognized and untreated pernicious anemia (Arch Intern Med 1996 May 27;156(10):1097.
    - Vitamin B12 deficiency affects about 5% of people aged 65-74 years and over 10% of people aged 75 years or older. (Age Ageing 2004; 33(1):34-41.
- Less common in other races
- Male to female ratio is 1:1
- Onset usually 40-70 yo
- Congenital form usually manifests in individuals < 2 yo

### **3. Risk factors**

- HLA-A2, A3, B7
- Type A blood
- European descent
- Associated with
  - Thyroid disorders, type 1 diabetes mellitus, ulcerative colitis
  - Addison's disease, infertility, acquired agammaglobulinemia

### **4. Morbidity/mortality**

- Pts. on appropriate therapy have normal lifespan

- Untreated disease can lead to permanent neurological dysfunction and CHF due to severe anemia
- Incidence of gastric adenocarcinoma is 2-3 times greater than in general population

## **Diagnostics**

### **1. History**

- Classic triad
  - Weakness, sore tongue, paresthesias
- Fatigue
- Weight loss and low-grade fever
- Constipation, loose stools, nausea, vomiting
- Clumsiness, unsteady gait, memory loss, irritability, personality changes

### **2. Physical exam**

- General
  - Pallor with premature whitening of hair and increased body girth
  - Beefy, red, smooth tongue
  - Low-grade fever and mild icterus
- Head, eyes, ears, nose & throat
  - Decreased visual and auditory abilities
  - Retinal hemorrhages and/or exudates (severe anemia)
- Cardiovascular
  - Tachycardia and/or flow murmurs
  - Dyspnea, tachypnea, and/or other signs of CHF (severe anemia)
- Hepatosplenomegaly
- Paresthesias in fingers or toes; loss of position and vibration sense
- Abnormal mental status (dementia, psychosis, depression)

### **3. Diagnostic testing**

- Laboratory
  - CBC
    - Macrocytic anemia, mild leukopenia, thrombocytopenia
  - Peripheral smear
    - Oval macrocytes, hypersegmented granulocytes, anisopoikilocytosis
  - LFTs
    - Elevated indirect bilirubin & LDH
      - Premature destruction of ineffectively produced RBCs
  - Serum cobalamin (vitamin B12)
  - Quantitative gastric secretion
    - Decreased total secretion, achlorhydric, absent or decreased intrinsic factor
  - Elevated serum methylmalonic acid and homocysteine
    - Elevated methylmalonic acid level more specific than elevated homocysteine level
    - Folic acid levels should be checked if isolated hyperhomocysteinemia
    - Falsely elevated in renal insufficiency
  - Normal RBC folate

- Other studies
    - Schilling test
      - Measures cobalamin absorption after an oral dose of radioactive cobalamin
      - Useful in demonstrating that anemia is caused by lack of intrinsic factor and not due to other causes of cobalamin deficiency
      - Expensive and not usually necessary to make diagnosis
    - Bone-marrow biopsy and aspiration
      - Show hypercellularity and megaloblastic changes
4. Diagnostic criteria
- Low vitamin B12 serum level
  - Elevated serum methylmalonic acid and homocysteine
  - Correction of vitamin B12 absorption in Schilling test after administration of B12 and intrinsic factor
  - Anti-intrinsic factor antibody and serum gastrin level permit diagnosis with 90-95% certainty (Am J Gastroenterology 2009 Aug;104(8):2071)

## **Differential Diagnosis**

### **1. Key differential diagnosis**

- Gastrointestinal
  - Achlorhydria (normal B12)
  - Alcoholic fatty liver, alcoholic hepatitis (liver USG, LFTs)
  - Celiac sprue (intestinal bx)
  - Cirrhosis (liver USG)
  - Gastric cancer (EGD)
  - Unconjugated hyperbilirubinemia (liver enzymes)
  - Atrophic gastritis (EGD)
  - Inflammatory bowel disease (colonoscopy & biopsy)
  - Malabsorption syndromes (specific absorption tests)
  - Tropical sprue (intestinal bx)
  - Zollinger-Ellison syndrome (stomach pH)
  - Blind loop syndrome
  - Diverticula/strictures
  - Vegetarian diet
  - Gastrectomy
  - Chronic pancreatitis (elevated amylase, lipase, pancreatic USG, CT)
  - Ileal mucosa disorder (intestinal bx)
- Hematologic
  - Folate deficiency (decreased RBC folate)
  - Iron-deficiency anemia (iron studies)
  - Immune thrombocytopenic purpura (low platelets bone marrow bx)
  - Aplastic anemia
  - Bone-marrow failure
  - Hemolytic anemia/other megaloblastic anemias
  - Macrocytosis
  - Myeloproliferative disease
  - Neutropenia

- Disorder of plasma transport of cobalamin/TCII deficiency (transcobalamine II assay; also known as holo TC assay)
- Psychiatric
  - Schizophrenia
- Endocrine
  - Hyperthyroidism, hypothyroidism
- 2. Extensive differential diagnosis
  - Neurologic
    - Alzheimer's disease
  - Infectious
    - Syphilis
    - Cestode infection/tapeworm infestation

### **Acute Therapy**

1. Transfusions rarely required for individuals with pernicious anemia unless pts. have severe CHF and/or CAD
2. Administration of cobalamin: 100 mcg IM qd
3. Administration of folic acid can make neurological symptoms worse

### **Chronic Care**

1. Cobalamin: 1000 mcg IM qd for 1 wk, followed by 1000 mcg IM qwk for 5-6 wk, then 1000 mcg IM every mo for life
  - Alternatively, 25-250 mcg/d PO (SOR:A)<sup>1</sup> References: The Cochrane Database of Systematic Reviews 2005, Issue 3. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency.

### **Follow-Up**

1. Refer to neurologist if unusual neurological manifestations
2. Admit to hospital for severe anemia
3. Continued outpatient visits are necessary to ensure pts. are responding to treatment and are receiving medication
4. Recommend all patients undergo gastroscopy shortly after being diagnosed with pernicious anemia. References: National Guideline Clearinghouse 2006 Jul 31:9306

### **Prognosis**

1. Early recognition and treatment provides a normal lifespan
2. Pts. not treated early in disease can have permanent neurological dysfunction

### **Prevention**

1. Pts. who have family members with pernicious anemia should have heightened recognition of development of anemia symptoms
2. Strict vegetarians should be counseled on taking maintenance vitamin B12 therapy
3. Although pts. with pernicious anemia have increased risk of gastric adenocarcinoma, asymptomatic individuals should not undergo periodic screening for development of malignancy since it has not been shown to increase lifespan

## References

1. Oh R, Brown DL: Vitamin B12 deficiency. *Am Fam Physician*. 2003 Mar 1; 67(5): 979-86.
2. Hoffman R, Benz EJ Jr, Shattil SJ: *Hematology: Basic Principles and Practice*. 3rd ed. New York, NY: Churchill Livingstone; 2000: 446-484.
3. Carmel R, Green R, Rosenblatt DS, Watkins D: Update on cobalamin, folate, and homocysteine. *Hematology* (Am Soc Hematol Educ Program). 2003: 62-81.

## Evidence-based Inquiries

1. How do we evaluate a marginally low B12 level?

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