Approach to Macrocytic /Megaloblastic Anemia

http://members.tripod.com/enotes/anemia-macrocytic.htmy

By means of morphologic and biochemical criteria, macrocytic anemias can be divided into two groups:

- **The megaloblastic anemias (the presence of hypersegmented neutrophils and oval macrocytes in the blood or of typical megaloblasts in the marrow)**

1. **The nonmegaloblastic anemias** (they simply represent macrocytic anemias in which DNA synthesis is unimpaired. They are macrocytic only occasionally; often they are normocytic. When macrocytosis is found, it tends to be mild; the MCV usually ranges from 100 to 110 fL and rarely exceeds 120 fL)

Diagnostic Approach

When confronted with a diagnostic problem involving macrocytic anemia, the physician should first try to distinguish between megaloblastic and nonmegaloblastic anemia. The most useful steps for this purpose are **morphologic examinations.**

A diagnosis of **megaloblastic anemia** can be made on the basis of **the presence of hypersegmented neutrophils and oval macrocytes in the blood or of typical megaloblasts in the marrow**.
These features are absent in patients with nonmegaloblastic, macrocytic anemia. In the latter group, the macrocytes tend to be round and often thin. Polychromatophilia and reticulocytosis may be prominent.

The nonmegaloblastic anemias comprise disorders characterized by an increased number of reticulocytes and those in which the reticulocytes are normal or decreased in number.

Macrocytosis is a common finding in clinical settings. In 1.7 to 3.6% of cases involving patients seeking medical care, MCV is increased, often in the absence of anemia.

Mild macrocytosis (MCV of 100 to 110 fL) is particularly common and often remains unexplained, even after careful study. Even so, this finding should not be ignored because it can be an important early clue to reversible disease. For example, it may appear 1 year or more before anemia develops in patients with pernicious anemia, and neurologic disease can progress during that interval.

In most surveys, the most common cause of macrocytosis is megaloblastic anemia. In four studies involving hospital inpatients with an increased MCV value, **30 to 50% of patients were deficient in folate, vitamin B12 , or both** . Many of the remaining individuals were being treated with chemotherapeutic agents that interfere with DNA metabolism.

Nonmegaloblastic anemias were most often associated with alcoholism and liver disease or with hemolytic anemia. Less commonly, they were noted in patients with a variety of refractory anemias.

Spurious macrocytosis can result from laboratory artifacts. Cold agglutinins , severe hyperglycemia, and marked leukocytosis can lead to a incorrect high MCV value. Care is

needed so that these situations do not lead to a fruitless search for a disorder known to cause macrocytic anemia.

CAUSES of Megaloblastic Anemia

1. Vitamin B12 deficiency
2. Folate deficiency
3. Combined folate and vitamin B12 deficiency
4. Inherited disorders of DNA synthesis
5. Drug- and toxin-induced disorders of DNA synthesis
6. Erythroleukemia

Vit. B_{12} deficiency

- macrocytosis, hypersegmented neutrophils, low plasma vit. B12 level.

Pernicious anemia is suggested by the finding of **Histalog fast achlorhydria, deficiency of intrinsic factor in gastric juice, positive anti intrinsic antibody in blood (in 75% of pts), anti parietal cell antibodies, also abnormal Schilling test** (poor oral absorption of the radioactive vit. B12 with urine excretion of <10% oral dose), which may be corrected with oral intrinsic factor administration (but pt should have several weeks of vit. B12 therapy first to improve ileal uptake)

Causes of Vit. B_{12} deficiency

A. Inadequate intake: strict vegetarianism (rare)
B. Malabsorption of Vit. B12
1. Low intrinsic factor:
- a. Pernicious anemia.
- b. Postgastrectomy or gastric bypass.
- c. Congenital absence or functional abnormality of intrinsic factor
2. Disorders of terminal ileum: Surgical resection, sprue, inflammatory bowel (Regional enteritis), neoplasms
3. Competition for vit. B12: fish tapeworm; Small-bowel bacterial overgrowth: Small-bowel diverticulosis, Anastomoses and fistulae, Blind loops and pouches, Strictures, Scleroderma, Achlorhydria
4. Drug: neomycin, colchicine, aminosalicylicacid

C. Transcobalamin II deficiency; Chronic disease of the pancreas; Zollinger-Ellison syndrome; Hemodialysis

Rx of Vit. B12 anemia:

1,000 ug IM monthly, or **PO Vitamin B_{12} 400 - 1000 ug tab/day** for patients with impaired absorption.

Folic acid deficiency

Causes of Folic acid deficiency

1. **Inadequate dietary intake**
2. **Folate Malabsorption**: acquired or congenital
3. **Increased requirement:** infancy, pregnancy, malignancy, hemolytic anemia
4. **Impaired metabolism:** alcohol, methotrexate, enzyme deficiency, etc.
5. **Drug-induced folate deficiency**
6. **Extensive intestinal resection, jejunal resection**

Rx of Folate deficiency: PO Folate 1-2 mg/day.

Combined folate and vitamin B12 deficiency

- Tropical sprue
- Gluten-sensitive enteropathy

Inherited disorders of DNA synthesis

- Orotic aciduria; Lesch-Nyhan syndrome; Thiamine responsive megaloblastic anemia
- Deficiency of enzymes required for folate metabolism: Methyl-tetrahydrofolate transferase, Formiminotransferase, Dihydrofolate reductase; Transcobalamin II deficiency; Abnormal transcobalamin II; Homocystinuria and methylmalonic aciduria

Drug- and toxin-induced disorders of DNA synthesis

- Folate antagonists (such as methotrexate)
- Purine antagonists (such as 6-mercaptopurine)
- Pyrimidine antagonists (such as cytosine arabinoside)
- Alkylating agents (such as cyclophosphamide)
- Zidovudine (AZT, Retrovir); Trimethoprim; Oral contraceptives; Anticonvulsants (such as Dilantin); Nitrous oxide; Arsenic; Chlordane

Nonmegaloblastic Macrocytic Anemias

- Disorders associated with accelerated erythropoiesis
- Alcoholism; Hepatic disease, Obstructive jaundice
- Hemolytic anemia, Posthemorrhagic anemia
- Disorders associated with increased membrane surface area (thin macrocytosis)

- Postsplenectomy
- Aplastic anemia; Acquired sideroblastic anemia; Refractory anemias
- Myelodysplastic anemias; Myelophthisic anemias
- Hereditary dyserythropoietic anemia, type 1
- Idiopathic macrocytosis in the elderly; Benign familial macrocytosis
- Hypothyroidism; COPD

Incidence of Various Macrocytic Anemias

- Alcohol abuse - 36%
- Vitamin B12 or folate deficiency - 21%
- Drug intake - 11%
- Accelerated erythropoiesis - 7%
- Liver disease - 6%
- Refractory anemias - 5%
- Hypothyroidism - 2%
- Unexplained - 12%
  Data from several sources quoted by Colon-Othero et al.

Miscellaneous Causes of Megaloblastic Anemia

A. Chemotherapeutic agents which interfere with DNA metabolism

1. Azathioprine, 6 mercaptopuriine, 5 fluorouracil
1. Cytosine arabinoside, procarbazine, hydroxyurea

B. Hereditary orotic aciduria & other rare metabolic diseases

C. Megaloblastiac anemias of unknown etiology

1. Refractory megaloblastic anemia
1. DiGuglielmo's syndrome

The Schilling urinary excretion test

By far the most popular method for testing vitamin B_{12} absorption has been **the Schilling urinary excretion test**, which is comparatively simple to perform. In this test, a so-called flushing dose of 1000 mug of nonradioactive vitamin B_{12} is injected intramuscularly at the same time as, or 1 to 2 hours after, 0.5 to 2.0 mug of the labeled vitamin is given orally. Radioactivity is assayed in a urine specimen collected for 24 to 72 hours thereafter. The purpose of the injection is to partially saturate body binding sites, thereby bringing about the urinary excretion of the vitamin that would otherwise be retained. A relatively constant proportion (about 34%) of the absorbed radioactive vitamin is excreted under these conditions. Some investigators have administered a second 1000-mug dose of nonradioactive vitamin B_{12} 24 hours after the first dose . This

procedure prompts the excretion of an additional small fraction of the absorbed vitamin; also, the accuracy of a subsequent test using added intrinsic factor is improved because the chance of contamination with label from the prior test dose is minimized.