Megaloblastic Anemia

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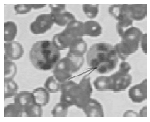
Updated on: 5 July 2016

- **Megaloblastic anemia** is one type of macrocytic anaeia that results from inhibition of DNA synthesis in red blood cell production.
- This is often due to deficiency of vitamin B12 and/or folic acid.
- Vitamin B12 deficiency alone will not cause the syndrome in the presence of sufficient folate.

- Megaloblastic anemia not due to hypovitaminosis may be caused by antimetabolites that poison DNA production directly, such as some chemotherapeutic or antimicrobial agents (for example azathioprine or trimethoprim).

- It is characterized by many large immature and dysfunctional red blood cells (megaloblasts) in the bone marrow and also by hypersegmented or multisegmented neutrophils (arrow).



- **Causes**
- Vitamin B12 deficiency:
  - achlorhydria-induced malabsorption
  - Deficient intake
  - Deficient intrinsic factor (pernicious anemia or gastrectomy)
  - Biological competition for B12 by diverticulosis, fistula, intestinal anastomosis, and infection by the marine parasite *Diphyllobothrium latum (fish tapeworm)*
  - Selective B12 malabsorption (congenital and drug-induced)
  - Chronic pancreatitis
  - Ileal resection and bypass

- Folate deficiency:
  - alcoholism
  - Deficient intake
  - Increased needs: pregnancy, infant, rapid cellular proliferation, and cirrhosis
  - Malabsorption (congenital and drug-induced)
  - Intestinal and jujenal resection
  - (indirect) Deficient thiamine and factors (e.g., enzymes) responsible for folate metabolism.

- Combined Deficiency (Tropical sprue): Vitamin B12 & folate.
- Inherited Pyrimidine Synthesis Disorders: Orotic aciduria
- Inherited DNA Synthesis Disorders
- Toxins and Drugs:
  - Folic acid antagonists (methotrexate)
  - Purine synthesis antagonists (6-mercaptopurine)
  - Pyrimidine antagonists (cytosine arabinoside)
  - Phenytoin
- Erythroleukemia

Hematological findings

The blood film can point towards vitamin deficiency:

- Decreased red blood cell (RBC) count and hemoglobin levels
- Increased mean corpuscular volume (MCV, >95 fl) and mean corpuscular hemoglobin (MCH)
- Normal mean corpuscular hemoglobin concentration (MCHC, 32-36 g/dL)
- The reticulocyte count is decreased due to destruction of fragile and abnormal megaloblastic erythroid precursor.
- The platelet count may be reduced.
- Neutrophil may show multisegmented nuclei ("senile neutrophil"). This is thought to be due to decreased production and a compensatory prolonged lifespan for circulating neutrophils, which increase numbers of nuclear segments with age.
- Anisocytosis (increased variation in RBC size) and poikilocytosis (abnormally shaped RBCs).
- Macrocytes (larger than normal RBCs) are present.
- Ovalocytes (oval-shaped RBCs) are present.
- Howell-Jolly bodies (chromosomal remnant) also present.

Blood chemistries will also show:

- In increased lactic acid dehydrogenase (LDH) level. The isozyme is LDH-2 which is typical of the serum and hematopoetic cells.
- Increased homocysteine and methylmalonic acid in B12 deficiency
- Increased homocysteine in folic defiency

- Normal levels of both methylmalonic acid and total homocysteine rule out clinically significant cobalamin deficiency with virtual certainty.
- Bone marrow (not normally checked in a patient suspected of megaloblastic anemia) shows megaloblastic hyperplasia.

Analysis

- The gold standard for the diagnosis of B12 deficiency is a low blood level of B12. A low level of blood B12 is a finding that normally can and should be treated by injections, supplementation, or dietary or lifestyle advice, but it is not a diagnosis.
- Hypovitaminosis B12 can result from a number of mechanisms, including those listed above. For determination of etiology, further patient history, testing, and empirical therapy may be clinically indicated.

- A measurement of methylmalonic acid can provide an indirect method for partially differentiating B12 and folate deficiencies. The level of methylmalonic acid is not elevated in folic acid deficiency.
- Direct measurement of blood cobalamin remains the gold standard because the test for elevated methylmalonic acid is not specific enough. Vitamin B12 is one necessary prosthetic group to the enzyme methylmalonyl-coenzyme A mutase.
- B12 deficiency is but one among the conditions that can lead to dysfunction of this enzyme and a buildup of its substrate, methylmalonic acid, the elevated level of which can be detected in the urine and blood.

- Due to the lack of available radioactive B12, the Schilling test is now largely a historical artifact.
- The Schilling test was performed in the past to help determine the nature of the vitamin B12 deficiency.
- An advantage of the Schilling test was that it often included B12 with intrinsic factor.