4th lecture in hematology by Dr.Alaa Fadhil Alwan

THE MEGALOBLASTIC ANEMIAS: COBALAMIN (VITAMIN B12) AND FOLATE DEFICIENCIES

The megaloblastic anemias result from interference in DNA synthesis. The most common causes of megaloblastic anemia in clinical practice are deficiencies of cobalamin (vitamin B12) and folic acid. Cobalamin deficiency can also be associated with neurologic abnormalities. It is important to differentiate between megaloblastic anemias and macrocytic anemias. Both are associated with an increase in red cell size (increased MCV), but whereas nearly all cases of megaloblastic anemia are macrocytic, many cases of macrocytic anemia are not megaloblastic. Common causes of macrocytic anemia include liver disease, reticulocytosis, and myelodysplastic syndrome

• Pernicious anemia is megaloblastic anemia due to autoimmune chronic gastritis with destruction of the gastric parietal cells. Pernicious anemia is not synonymous with megaloblastic anemia; it is a subset of megaloblastic anemias**.**

Macrocytic Anemias: Megaloblastic versus Non-Megaloblastic

Megaloblastic	**Non-Megaloblastic**
Folate deficiency	Liver disease
Cobalamin deficiency	Myelodysplasia
Antifolate drugs	Reticulocytosis
Cancer chemotherapy	Hypothyroidism
	Alcoholism
	(COPD)

Folic Acid

Folic acid (folate) is actually pteroylglutamic acid. it is abundant in vegetables, fruit, cereals, and dairy products. Folic acid is heat labile, and much is destroyed by cooking. Therefore, the primary dietary source for folic acid is fresh uncooked fruits and vegetables. It is primarily absorbed in the jejunum. The body has stores of approximately 5 to 10 mg. Folate stores can be exhausted in a few weeks to a few months—much faster if the enterohepatic circulation is disrupted. Pregnancy is worth special mention here. It is believed that folate deficiency during pregnancy predisposes the fetus to neural tube defects and that folate supplementation will reduce the risk of such defects. Every woman who is pregnant, or who is considering becoming pregnant, should take folic acid

Causes of Folate Deficiency
Inadequate Diet (most common)
Alcoholism
Lack of fresh fruits and vegetables
Malabsorption (less common)
Gluten-sensitive enteropathy (celiac sprue)
Tropical sprue
Extensive small bowel resection
Inflammatory bowel disease (regional enteritis)
Rare Causes
Hemodialysis
Antiepileptic drugs
Antifolate drugs
Increased requirements: chronic hemolytic anemia, psoriasis, pregnancy
Oral contraceptives (uncommon)
Exposure to nitrous oxide (N_2O)

Cobalamin(B12)
The primary dietary sources of cobalamin are meat, eggs, milk, and cheese. The daily requirement is ~0.1 microgram/day. Thus, body stores can supply daily needs for many years. Absorption of cobalamin from the GI tract is a multistep process, with several places for possible problems. Absorption requires intrinsic factor (IF), which binds to B12. There are specific receptors for the IF-B12 complex in the terminal ileum. B12 bound to IF is efficiently absorbed, but very little unbound B12 can be absorbed. Intrinsic factor is produced by gastric parietal cells, which also produce gastric acid. Dietary B12 is bound to proteins and must first be released by gastric acid and proteases.

Causes of Cobalamin Deficiency
Malabsorption (most common)
Pernicious anemia: loss of IF production and gastric acid
Gastrectomy: loss of IF production and gastric acid
Inflammatory bowel disease: loss of absorption in terminal ileum
Resection of terminal ileum: loss of absorption by specific IF-B12 receptors
Pancreatic insufficiency: inability to digest R-binders off of B12
Blind loop syndrome: bacterial overgrowth; bacteria compete for B12
Congenital deficiency of intrinsic factor (rare)
Fish tapeworm (Diphyllobothrium latum): competition for B12
Dietary Deficiency (extremely rare in US)
Strict vegans
Infants breast-fed by vegetarian mothers
Congenital Deficiency of Transcobalamin

The most common cause of cobalamin deficiency is pernicious anemia. Pernicious anemia is an autoimmune chronic gastritis, resulting in destruction of the parietal cells and loss of IF production. It occurs in all ethnic groups, although the highest incidence appears to be in persons of Scandinavian, English, Scottish, and Irish descent. In Caucasians, the average age of onset is about 60 years, although it can be seen at all ages, including children. There is also a strong association between

pernicious anemia and other autoimmune disorders, including thyroid disease (Graves' disease, Hashimoto's thyroiditis), Addison's disease, vitiligo, and hypoparathyroidism. Patients with pernicious anemia may have serum antibodies against gastric parietal cells (anti–parietal cell antibodies) or antibodies against intrinsic factor (anti-IF antibodies). Patients with pernicious anemia have an increased risk of gastric carcinoma compared to the general population; the increase in risk is significant, but the overall risk for the individual patient is low.

Symptoms

Megaloblastic anemia presents with an insidious onset of weakness, fatigue, abdominal pain, nausea, diarrhea, or constipation. Patients may complain of soreness of the tongue or mouth or pain on swallowing. Weight loss is common . Since the onset of anemia is gradual, allowing time for physiologic compensation, patients often tolerate unusual degrees of anemia without symptoms.

Physical Examination

Physical examination characteristically shows pallor and a peculiar "lemon yellow" coloration of the skin (due to mild hyperbilirubinemia). A "beefy" red tongue is common. Cobalamin deficiency may be complicated by neurologic disease, a feature that separates cobalamin from folate deficiencies. The degree of neurologic disorder does not correlate with the degree of anemia, and patients may have severe neurologic disease without significant hematologic abnormalities. The primary neuropathologic change in cobalamin deficiency is demyelination of the dorsal and lateral columns of the spinal cord and the cerebral cortex. Both sensory and motor systems are affected, leading to the terms subacute combined degeneration and combined system disease. The earliest and most common symptom is paresthesias in the distal extremities. The earliest changes seen on physical examination are decreased vibration and position sensation in the extremities. These symptoms progress to weakness, clumsiness, and an unsteady gait. In severe disease, the patient may have severe weakness and spasticity. In more advanced cases, the patients may have hyperreflexia, clonus, and positive Romberg and Babinski signs. Early cerebral signs include depression and impairment of memory.

More severe cortical changes include delusions, hallucinations, and paranoid and schizophrenic states (megaloblastic madness); however, these are uncommon.

Laboratory Evaluation

The CBC shows anemia, which can be quite striking. The MCV is increased (often >120 fL). The white cell count and platelet count are typically decreased, but usually to a lesser degree than the hemoglobin. On blood film erythrocytes show macrocytosis; the presence of oval macrocytes is very suggestive of megaloblastic anemia. The characteristic finding in granulocytes is hypersegmented neutrophils. Hypersegmented neutrophils are defined by the Rule of Fives: either more than five distinct nuclear lobes in any cell or >5% of neutrophils have five distinct nuclear lobes.

• Hypersegmented neutrophils are one of the earliest blood findings of megaloblastic anemia and may precede both anemia and macrocytosis. They are also one of the last morphologic changes to disappear after therapy is started (several days to 2 weeks). The presence of hypersegmented neutrophils in a patient with a macrocytic anemia is a strong indication that the process is megaloblastic anemia.

The marked intramedullary hemolysis results in an increase in serum lactic dehydrogenase (LDH) and bilirubin and a decrease in serum haptoglobin

Laboratory Diagnosis of Megaloblastic Anemias

Test	Cobalamin Deficiency	Folate Deficiency
Serum cobalamin	Decreased	Usually normal
Serum folate	Normal to increased	Decreased
Erythrocyte folate	Decreased	Decreased
Serum methylmalonic acid	Increased	Normal
Serum homocysteine	Increased	Increased (moderately)

*The Schilling
*Assay of serum anti–parietal cell or anti-IF antibodies can also be useful in diagnosis of pernicious anemia:
*Anti–parietal cell antibodies are very sensitive for pernicious anemia (~90%) but are not very specific. They are found in about 8% of normal older individuals and 50 to 60% of patients with atrophic gastritis not associated with pernicious anemia.
*Anti-IF antibodies are very specific for pernicious anemia but not very sensitive (~50–60%).

Investigations that may be needed in patients with macrocytosis

• Serum vitamin B12 assay
• Serum and red cell folate assays
• Liver and thyroid function
• Reticulocyte count
• For vitamin B12 deficiency: serum parietal cell and intrinsic factor antibodies, radioactive vitamin B12 absorption with and without intrinsic factor (Schilling test), possibly serum gastrin concentration
• Serum antigliadin and anti-endomysial antibodies
• Consider bone marrow examination for megaloblastic changes suggestive of vitamin B12 or folate deficiency, or alternative diagnoses—eg myelodysplasia, aplastic anemia, myeloma
• Endoscopy—gastric biopsy (vitamin B12 deficiency); duodenal biopsy (folate deficiency)

Treatment of Megaloblastic Anemia

It is critical to determine whether the deficiency is due to folic acid or cobalamin; giving the wrong treatment is ineffective and potentially dangerous. Oral folate supplementation is the treatment of choice for most cases of folate deficiency. Treatment of pernicious anemia and other causes of cobalamin malabsorption requires parenteral therapy. Available preparations include cyanocobalamin and hydroxocobalamin. A typical treatment regimen would be 1,000 microg (1 mg) of cyanocobalamin daily for 7 day then weekly for 4 weeks, followed by monthly for life.
The response to therapy is usually dramatic, with rapid symptomatic improvement. Reticulocytosis should appear after about 2 to 3 days, with a maximum response at 5 to 8 days. The hemoglobin should begin to rise after about 1 week, with normalization

of the hemoglobin by 4 to 8 weeks. The granulocyte count usually reaches a normal level within 1 week; hypersegmentation of neutrophils usually disappears within 2 weeks. The platelet count usually returns to normal within 1 week. The bone marrow shows dramatic improvement, with disappearance of megaloblasts within 1 to 2 days. The serum LD and bilirubin drop rapidly.

• It is important to monitor the response to therapy; failure to respond appropriately indicates either an incorrect diagnosis or some complicating factor such as coexistent iron deficiency.