MACROCYTIC ANEMIA

Anemia

Anemia is a deficiency of plasma Hb concentration due to decreased number of circulating RBCs or an abnormally low total Hb content per unit volume of blood.

Nutritional anemias are caused by dietary deficiencies of Iron, Vitamin B_{12} or Folic acid.

Anemia can also be caused by chronic blood loss, bone marrow abnormalities, increased hemolysis, infections, malignancy, endocrine deficiencies, and a number of other disease states.

A number of drugs also cause toxic effects on blood cells, HB production, or erythropoietic organs, leading to anemia.

Types of Anemias

Anemias are classified according to their pathophysiologic basis, such as whether related to diminished production or increased loss of RBCs, or according to cell size.

Microcytic Anemias

Iron deficiency

Thalassemia

Anemia of chronic disease

Macrocytic Anemias

Megaloblastic (Vit. B_{12} and Folate deficiency)

Nonmegaloblastic (Chemotherapy, Antiretrovirals, Liver disease, Increased reticulocytosis, Myxedema)

Folic Acid

Folic acid is necessary for the transfer of one-carbon fragments in the synthesis of purine and pyrimidine bases.

Folic acid is also known as pteroylglutamic acid. It is readily absorbed from the gastrointestinal tract.

Only modest amounts are stored in the body, so a decrease in dietary intake is followed by anemia within a few months.

Anemia is usually the first sign of folic acid deficiency because of the need for continuous production of red cells.

Pharmacodynamics

Folic acid is necessary for the transfer of one-carbon fragments in the synthesis of purine and pyrimidine bases.

It is most important in the health of rapidly dividing cells, in which DNA must be rapidly synthesized.

Deficiency of folic acid during pregnancy increases the risk of neural tube defects in the fetus (congenital abnormalities).

Folate deficiency results in Megaloblastic anemia.

Folate deficiency may be caused by:

1. Increased demand (pregnancy, lactation, hemolytic anemia)

2. Dietary deficiency or poor absorption

3. Drugs, such as DHFR inhibitors, e.g. Phenytoin, Methotrexate, Trimethoprim

Alcoholics and patients with liver disease develop folic acid deficiency due to poor diet and diminished hepatic storage of folate.

It is most important in the health of rapidly dividing cells, in which DNA must be rapidly synthesized.

Clinical Uses and Toxicity

Folic acid deficiency is most often caused by dietary insufficiency or by malabsorption.

Anemia due to folic acid deficiency is readily treated by oral folic acid supplementation.

Folic acid supplements also correct the anemia but not the neurologic deficits of vitamin B12 deficiency.

Vitamin B12 deficiency must be ruled out before selecting folic acid as the sole therapeutic agent in megaloblastic anemia.

Oral folic acid (1 mg/d) is readily absorbed even in patients with malabsorption syndrome and is sufficient to treat megaloblastic anemia.

Cyanocobalamin (Vit. B_{12})

Vitamin Bl2 (cobalamin), a cobalt-containing molecule, along with folic acid, is a cofactor in the transfer of one-carbon units, a step necessary for the synthesis of DNA.

Impairment of DNA synthesis affects all cells, but because red blood cells must be produced continuously, deficiency of either Bl2 or folic acid usually manifests first as anemia.

Vitamin Bl2 is produced only by bacteria; this vitamin cannot be synthesized by multicellular organisms.

All foods of animal origin contain sufficient Vit. B_{12} and daily absorption is about 5 μg.

Vit. B_{12} binds to intrinsic factor, a protein secreted by gastric parietal cells. Vit. B_{12}- intrinsic factor complex is absorbed from terminal ileum, transported in plasma by transcobalamins I and III and stored in the liver.

Daily losses of Vit. B_{12} from the body are 3-5 μg.

Vitamin Bl2 is stored in the liver in large amounts (2000-5000 μg); a normal individual has enough to last 5 years, and deficiency develops more than 3 years after its absorption ceases.

(Intrinsic factor deficiency results in 'Pernicious anemia')

Low dietary intake or poor absorption contribute to its deficiency. Nonspecific malabsorption syndrome and gastric resection can also cause Vit. B_{12} deficiency.

This Vitamin can be administered orally, intramuscularly or deep subcutaneously.

Megaloblastic anemia due to B_{12} deficiency can be differentiated from one due to folic acid deficiency by the neurological symptoms.

Concurrent treatment with folic acid is recommended.

Two available forms of vitamin B12 cyanocobalamin and hydroxo-cobalamin, have similar pharmacokinetics, but hydroxocobalamin is more firmly bound to plasma proteins and has a longer circulating half-life.

Pharmacodynamics

Vitamin B12 is essential in two reactions:

Conversion of methyl-malonyl-CoA to succinyl-CoA and

Conversion of homocysteine to methionine.

The 1st reaction is essential for lipid metabolism; a deficiency of vitamin B12 results in abnormalities of the lipids essential for normal neuronal function.

The 2nd reaction, conversion of homocysteine to methionine, is linked to folic acid metabolism and DNA synthesis.

Clinical Uses and Toxicity

Treatment of naturally occurring **pernicious anemia** and anemia caused by gastric resection.

Because Bl2-deficiency anemia is almost always caused by inadequate absorption, therapy should be parenteral.

Oral therapy may suffice for maintenance, but massive doses must be used.

In plasma B12 is transported by binding to transcobalamin II, a glycoprotein.

When parenteral vitamin B12 is given, any in excess of the transport protein binding capacity (about 50-100 micrograms) is excreted.

Vitamin B12 deficiency leads to the development of neurologic defects, which may become irreversible if not treated promptly.

Treatment is by replacement of vitamin B12 using parenteral therapy.

Hydroxocobalamin binds cyanide ion to form cyanocobalamin, hydroxocobalamin has also been used to treat **cyanide toxicity** caused by nitroprusside.

Neither form of vitamin B12 has significant toxicity.