LEC 6

Megaloblastic Aneamia

Megaloblastosis is a generalized disorder involving most rapidly growing cells, such as gastrointestinal and uterine cervical mucosal cells. The etiology of megaloblastosis is various, but a common basis is impaired DNA synthesis. The most common causes of megaloblastosis are cobalamin (vitamin B-12) and folate deficiency.

Serious organ failure can occur in individuals with megaloblastosis. Both vitamin B-12 and folate deficiencies can cause memory loss, depression, personality changes, and psychosis, as well as peripheral neuropathy. Vitamin B-12 deficiency can cause sub-acute combined dorsal and lateral spinal column degeneration .

Major causes for cobalamin deficiency :

The daily requirement cobalamin is about 5-7 µg/d. As mentioned, large amounts of cobalamin are stored in liver and other sites. Therefore, cobalamin deficiency only develops about 3-4 years after the stop of cobalamin uptake.

1 - Dietary cobalamin deficiency in strict vegetarians who avoid meat, eggs, and dairy products.

2 - Atrophic gastritis commonly occur in elderly persons. These conditions are responsible for the impaired release of protein-bound cobalamins and, hence, can interfere with cobalamin uptake.

3 - Pancreatic enzymes are not available to help the release of cobalamins from R-proteins and thus cobalamins are not absorbed.

4 - Disorders of the terminal ileum can result in cobalamin deficiency. Because the terminal ileum is the site of uptake of cobalamin-IF complexes .

5 - Nitrous oxide exposure can cause megaloblastosis by oxidative inactivation of cobalamin. Prolonged exposure to nitrous oxide can lead to severe mental and neurological disorders.

A partial list of medications that can cause cobalamin deficiency includes purine analogs (6-mercaptopurine, 6-thioguanine, acyclovir), pyrimidine analogues (5-fluorouracil, 5-azacytidine, zidovudine), ribonucleotide reductase inhibitors (hydroxyurea, cytarabine arabinoside), and drugs that affect cobalamin metabolism (*p* -aminosalicylic acid, phenformin, metformin).

Major causes for folate deficiency :

The daily requirement for adults is about 0.4 mg/d. Storage is limited, and folate deficiency develops about 3-4 weeks after the stop of folate intake.

1 - Dietary folate deficiency is a cause. most people obtain sufficient folate from fortified foods. The preparation of foods is a major cause for folate deficiency, especially in elderly persons. Folates are very thermolabile. Therefore, excessive heating can lead to inactivation, especially when foods are diluted in water.

2 - Failure to increased folate supplementation in response to increased demand can result in deficiency. There is an increased need for folate in the face of hemolysis, pregnancy, lactation, rapid growth .

3 - Intestinal disorders that impede folate absorption include tropical sprue, nontropical sprue (celiac disease or gluten sensitivity), amyloidosis, and inflammatory bowel disease.

A partial list of medications that can cause folate deficiency includes phenytoin, metformin, phenobarbital, dihydrofolate reductase inhibitors (trimethoprim, pyrimethamine), methotrexate and other antifolates, sulfonamides (competitive inhibitors of 4-aminobenzoic acid), and valproic acid.

Other causes for megaloblastosis :

1 - Megaloblastosis in HIV infection and myelodysplastic disorders is due to a direct effect on DNA synthesis in hematopoietic and other cells.

2 - Patient's history might reveal anemia and neurological abnormalities. Some patients can have gastrointestinal symptoms such as loss of appetite, weight loss, nausea, and constipation. Patients may have a sore tongue and canker sores.

A spectrum of mental changes, from a change in personality to psychosis, as well as peripheral neuropathy, can occur in both folate and cobalamin deficiencies.

Peripheral neuropathy presents as numbness, pain, tingling, and burning in a patient's hands and feet. Patients may report loss of sensation and that they feel like they are wearing a thin stocking or glove.

History findings to help identify folate deficiency are as follows:

1. Poor nutrition, alternative diets, and excessive heating of foods.
2. Chronic alcoholism .
3. Conditions that interfere with folate absorption, including inflammatory bowel disease, sprue or gluten sensitivity, and amyloidosis.

4. Conditions that increase folate consumption, such as pregnancy, lactation, hemolytic anemia, hyperthyroidism .
5. Hyper alimentation and hemodialysis .
6. Medications that affect folate .
7. Hereditary disorder .

History findings to help identify a cobalamin deficiency are as follows:

1. Abdominal discomfort, reflux, early satiety, and abdominal bloating: This condition can impair cobalamin absorption.
2. History of a gastrectomy: This would suggest the possibility of insufficient production of intrinsic factor.
3. Conditions that affect the terminal ileum (site of cobalamin absorption), such as inflammatory bowel disease, sprue, or ileal resection
4. A history of folate administration without vitamin B-12 therapy.
5. A history of megaloblastosis since childhood: This would suggest a hereditary cause of cobalamin deficiency.

Physical Examination :

1 - Evidence of anemia can include patients who are pale and weak but otherwise a symptomatic, particularly if the anemia had developed gradually and is compensated. In severe anemia, patients may have dyspnea, tachycardia, and cardiopulmonary distress.

2 - Patients may have a lemon-yellow hue due to the combination of anemia and an increased indirect bilirubin level. The source of the bilirubin is intramedullary hemolysis.

3 - Glossitis, characterized by a smooth tongue due to loss of papillae, occurs in persons with cobalamin deficiency.

4 - Dermatologic signs include hyper pigmentation of the skin and abnormal pigmentation of hair due to increased melanin synthesis.

5 - Abdominal scars may suggest a blind loop syndrome due to gastric surgery or a lack of ileal absorption of cobalamin in a patient who had an ileal resection.

6 - Patients with non tropical and tropical sprue may have signs of malabsorption, such as weight loss, abdominal distention, diarrhea, and steatorrhea. These patients often have metabolic bone disease or bleeding resulting from to deficiencies in vitamin K–dependent factors.

7 - Patients who have megaloblastosis as a result of HIV infection or myelodysplastic syndromes usually have signs of these disorders.

8 - Children with inborn errors associated with folate and cobalamin deficiencies may have signs of these hereditary disorders.

Tests to Diagnose Cobalamin and Folate Deficiencies : -

1 - Serum vitamin B-12 and RBC folate levels .
2 - Serum homocysteine and methylmalonic acid levels .
3 - Parietal cell and intrinsic factor antibodies .
4 - Schilling test : (a radiometric test) .
5 – MCV. > 95 % (120 – 140 fl. In severe cases) .
6 – MCH. Is raise .
7 – MCHC. Is normal .
8 – Blood film : macrocytosis , polychromasia , hypersegmented Neutrophil , normoblast , poikilocytosis, Anisocytosis .
9 – Platelets count : moderately reduced .
10 – Reticulocyte count : low .
11 – Hb. And RBCs count : Decreased