**Macrocytic anaemia**

**Objectives:**

1-Define macrocytic anaemia and its causes.

2-Define megaloblastic anaemia and its causes

3- Know the dietary sources,daily requirement, site of absorption and function of folate and B12 in the body.

4-Know the causes for B12 and for folate deficiency.

5-Know the clinical and laboratory features of megaloblastic anaemia.

6-Enumerate causes of macrocytosis other than megaloblastic anaemia

In **macrocytic anaemia** the red cells are abnormally large.

**Causes of macrocytic anaemia:**

1-megaloblastic :B12 or folate deficiency

2- non-megaloblastic:e.g. alcohol, liver disease e.t.c.

**Megaloblastic anaemias**

-This is a group of anaemias in which the erythroblasts in the bone marrow show a characteristic abnormality, maturation of the nucleus being delayed relative to that of the cytoplasm.

-The underlying defect is defective DNA synthesis and in **clinical practice this is usually caused by deficiency of vitamin Bl2 or folate.**

-Less commonly, due to abnormalities of metabolism of these vitamins or other lesions in DNA synthesis.

* **Vitamin B12 (B12** **cobalamin)**

-This vitamin is derived from animal products in the diet such as liver, meat, fish and dairy products

-The daily requirement is about( 1μg).

-The main loss of B12 from the body is in the bile.

-Dietary vitamine B12 is released from food by the action of hydrolytic acid and peptic enzymes

.- Bl2 is combined with the glycoprotein intrinsic factor (IF)

(which is synthesized by the gastric parietal cells) to form the IF- Bl2 complex .**In the distal ileum Bl2 is absorbed** and IF destroyed.

-In the plasma vitamine B12 is transported and delivered to the cells by **transcobalamin.**

- **Vitamine B12 is essential for two metabolic pathways:**

**1.** It is a coenzyme in the conversion of 5-methyl-tetrahydrofolate to hydrofolate and the simultaneous conversion of homocystine to methionine ,this pathway is **essential for synthesis of DNA and RNA**.

**2.**It is a coenzyme for the synthesis of succinyl coenzyme A, a necessary step in catabolism of some fatty acids and amino acids.



**Causes of vitamin B12 deficiency:**

1-**Nutritional**

Especially vegans

**2-Malabsorption**

*. Gastric causes*

Pernicious anaemia

Congenital lack or abnormality of intrinsic factor

Total or partial gastrectomy

*. Intestinal causes*

Chronic tropical sprue

Ileal resection and Crohn's disease

Fish tapeworm

**Pernicious anaemia:**

-An autoimmune attack (autoantibodies) on the gastric mucosa leading to gastric atrophy with loss of secretion of pepsin,acid and intrinsic factor with resultant vitamine B12 deficiency.

-Autoantibodies against gastric parietal cells mainly or against intrinsic factor.

-Female ,Blue eyes, Early greying

-Northern European

-Familial

-Blood group A

-there may be associated autoimmune disease like Vitiligo, Myxoedema,

Hashimoto's disease and other s.

-There is also an increased incidence of carcinoma of the stomach

* **Folic Acid:**

-Folic acid is derived from the diet. Rich dietary sources include fruit and vegetables (particularly green vegetables) , liver ,kidney ,yeast .

-Dietary folate is absorbed maximally in the **upper jejunum.**

-The folate in the body is mainly in the form of polyglutamates .

-The role of folate is the transfer of single carbon groups. It is essential for the synthesis of purines and pyrimidines and for inteconversions of various amino acids.

**Causes of folate deficiency.**

-**Nutritional**

Especially old age, poverty, goat's milk anaemia, etc.

-**Malabsorption**

Tropical sprue, gluten-induced enteropathy (adult or

child).

**-Excess utilization**

Pregnancy and lactation, haemolytic anaemias , Malignant disease, Inflammatory diseases: Crolm's disease, tuberculosis.

**-Drugs**

Anticonvulsants, sulfasalazine

**- Liver disease, alcoholism**

**The mechanism of megaloblastic anaemia in vitamine B12 deficiency is actually a functional folate deficiency .When B12 is deficient there is reduced conversion of 5-methyl-tetrahydrofolate to hydrofolate,the form that can be polygutamated and can participate in pathways leading to DNA and RNA synthesis.**

**Clinical features of megaloblastic Anaemia:**

-symptoms and signs of anaemia**.**

-mild jaundice (lemon yellow tint) because of the excess breakdown of

haemoglobin resulting from increased ineffective erythropoiesis in the bone marrow.

-Glossitis , angular stomatitis.

- Mild symptoms of malabsorptionand loss of weight may be present because ofthe epithelial abnormality**.**

**- In vitamine B12 deficiency ,** recognised neurological features include peripheral neuropathy ,subacute combined degeneration of the spinal cord ,dementia,psychiatric manifestation and optic atrophy .

-Folate or B12 deficiency in the mother predisposes to neural tube defect (NTD) (anencephaly, spina bifida or encephalocoele) in the fetus.

-Other tissue abnormalities

Sterility is frequent in either sex with severe B12 or folate deficiency. Macrocytosis and other morphological abnormalities of cervical, buccal, bladder and other epithelia occur.

**Laboratory findings**

-The anaemia is macrocytic (high MCV).

- the macrocytes are typically oval in shape (oval macrocytes).

-the total white cell and platelet counts may be moderately reduced, especially in severely anaemic patients.

-A proportion of the neutrophils show hypersegmented nuclei (with six or more lobes).

-The reticulocyte count is low .

-**The bone marrow** is usually hypercellular and the erythroblasts are large and show failure of nuclear maturation maintaining an open, fine, lacy primitive chromatin pattern but normal haemoglobinization. Giant and abnormally shaped metamyelocytes are characteristic.

-The serum unconjugated bilirubin and lactate dehydrogenase (LDH) are raised.

-Assay serum B12 , and serum and red cell folate to confirm diagnosis.

-Tests for cause of vitamin B12 or folate deficiency.

* **Causes of macrocytosis other than megaloblastic anaemia:**

1.Alcohol

2.Liver disease

3.Myxoedema

4.Myelodysplastic syndromes

5.Cytotoxic drugs

6.Aplastic anaemia

7.Pregnancy

8.Smoking

9.Reticulocytosis

10.Myeloma .

11.Neonatal**.**