Notes

# 17

# MACROCYTIC ANEMIAS

## 17.1 INTRODUCTION

Macrocytic anemias are characterized by the presence of macrocytes (RBC >9µm in diameter) with normal haemoglobin content. Examples of Macrocytic anemias are Megaloblastic anemia due to deficiency of cobalamin or folic acid, Aplastic anemia, Anemia in liver disease and hypothyroidism, Anemia in myelodysplastic syndrome

## OBJECTIVES

After reading this lesson, you will be able to:

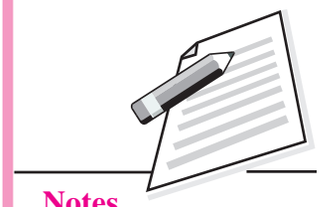
- define macrocytic anemias
- describe megaloblastic anemia
- explain laboratory diagnosis of megaloblastic anemias
- discuss the other causes of macrocytosis in brief

## 17.2 DEFINITION

Macrocytic anemias are characterized by the presence of macrocytes (RBC >9µm in diameter) with normal haemoglobin content. The MCV and MCH are increased, and MCHC is normal.

### Examples

- Macrocytic anemia is further divided into megaloblastic and nonmegaloblastic anemia
- Examples of megaloblastic anemia are folic acid or vitamin B12 deficiency, inherited disorders of DNA synthesis and drug induced disorders of DNA synthesis.





- Nonmegaloblastic anemia can be due to hypothyroidism, liver disease, alcoholism and aplastic anemia

## 17.3 MEGALOBLASTIC ANEMIA

### 17.3.1 Definition

These are a group of disorders due to defective DNA synthesis and nuclear cytoplasmic asynchrony resulting in anemia with abnormally large red cells.

### 17.3.2 Cause of Megaloblastic Anemia

For normal DNA synthesis vitamin $B_{12}$ or cobalamin and folic acid are essential. Megaloblastic anemia occurs due to the deficiency of either or both of these vitamins.

### 17.3.3 Pathogenesis

In megaloblastic anemia there is a defect in DNA synthesis, RNA synthesis remains unimpaired. There is impaired cell division due to which hemoglobin is synthesized in excess during the delay. As a result of this enlarged erythroid precursors are produced. These changes affect all proliferating cells.

## 17.4 VITAMIN $B_{12}$ OR CYANOCOBALAMIN

### 17.4.1 Source

This vitamin is synthesized only by micro organisms and is stored in animal tissue especially the liver. A strict vegetarian diet is deficient in this vitamin.

### 17.4.2 Absorption

Vitamin $B_{12}$ is called the EXTRINSIC FACTOR. It is present in food bound to proteins. The acidic pH of the gastric juices is needed to release it from protein. At this pH, it binds to the salivary R PROTEIN (haptocorrin). The parietal cells of the stomach mucosa secrete another protein called the INTRINSIC FACTOR (IF). The R PROTEIN- cobalamin complex and IF pass into the duodenum. In the duodenum, pancreatic secretions neutralize the pH and provide the enzymes that degrade R PROTEIN. The cobalamin binds to IF. The complex passes through the rest of the duodenum and jejunum. In the ileum there are receptors in the mucosa for IF. The cobalamin is absorbed by endocytosis and it then binds to a transport protein called TRANSCOBALAMIN II. (TCII)

### 17.4.3 Transport in plasma

The cobalamin is transported in plasma by the TC II – cobalamin complex.

### 17.4.4 Entry into cells

Cells have receptors for TC II. The TCII binds to the receptor and the cobalamin is internalized.

### 17.4.5 Enterohepatic Circulation of Cobalamin

0.5 - 9 µg of cobalamin bound to TC II is taken up by hepatocytes which have receptors for TCII and the cobalamin is secreted into bile. Most of this cobalamin is reabsorbed from the intestinal tract.

### 17.4.6 Excretion

The daily excretion of cobalamin is ~1 µg.

### 17.4.7 Requirements

The daily intake of cobalamin is 2 – 5 µg/day. The normal serum concentration is 180 – 640 ng/L

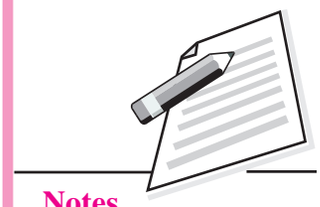
### 17.4.8 Causes of Vitamin $B_{12}$ Deficiency

1. Dietary insufficiency. The pure vegetarian Indian diet contains very little cobalamin. Deficiency is also seen in old and bed ridden patients.
2. Increased requirements – pregnancy, lactation, growing children, hemolytic anemia.
3. Inability to absorb the vitamin – following gastric surgery, lack of hydrochloric acid in gastric juice, drugs suppressing acid production, lack of intrinsic factor due to auto antibodies to parietal cells or intrinsic factor, ileal resection, chronic diarrhea.
4. Competitive absorption of the vitamin by fish tape worm and bacteria in blind loop syndrome.

## 17.5 FOLIC ACID OR PTEROYL MONOGLUTAMIC ACID

### 17.5.1 Sources of Folic Acid

This vitamin if present in animal sources like milk, eggs, liver and in vegetable sources like fresh green vegetables, fruits and yeast. It is destroyed by prolonged cooking.





### 17.5.2 Absorption

Polyglutamates are broken down to monoglutamates and folic acid is absorbed in the small intestine, mainly the jejunum with the help of folate binding proteins.

### 17.5.3 Transport

There is no specific serum transport protein. It is bound loosely to serum albumin.

### 17.5.4 Entry into Cells

Cells have receptors for folate binding proteins. The folic acid is transported into the cell in vesicles.

### 17.5.5 Enterohepatic Circulation of Folic Acid

There is an enterohepatic circulation of folic acid similar to cobalamin.

### 17.5.6 Excretion

Approximately 200 µg of folate is excreted focally every day.

### 17.5.7 Requirements

The recommended dietary folate equivalent intake is 400 µg/day for adults, 600 µg/day in pregnant women and 500 µg/day in lactating women.

The normal serum folate is 3 - 20 µg/L

The normal red cell folate is 160 - 640 µg/L.

Dietary folate which enters the blood stream is rapidly cleared to the tissues. The serum folate is labile and is sensitive to short term changes in folic acid levels. In these situations it is better to assay the red cell folate level which will give a better assessment of tissue folate stores.

### 17.5.8 Causes of Folic Acid Deficiency

1. Dietary insufficiency: Deficiency is seen in old and bed ridden patients, ICU patients and by eating over cooked food.
2. Increased requirements – pregnancy, lactation, growing children, hemolytic anemia
3. Liver disease and chronic alcoholism
4. Inability to absorb the vitamin – following gastric surgery, sprue, chronic diarrhea, malabsorption.
5. Drugs – several chemotherapy drugs which are folic acid antagonists.

## 17.6 CLINICAL FEATURES OF MEGALOBLASTIC ANEMIA

There is moderate to severe anemia, pallor, breathlessness, mild jaundice, premature graying of hair, bald tongue, glossitis, angular stomatitis, and pigmentation of knuckles. Patient complains of tingling and numbness of hands and feet and poor memory. In severe megaloblastic anemia neurological symptoms may appear. Folic acid deficiency in early pregnancy leads to defective development of the nervous system resulting in congenital defects in the baby called neural tube defects.

## 17.7 LABORATORY DIAGNOSIS OF MEGALOBLASTIC ANEMIA

The features of megaloblastic anemia in both cobalamin and folate deficiency are similar and the two can only be differentiated by assay of the vitamins in blood.

### 17.7.1 Complete Blood Count

1. Hemoglobin, PCV and RBC count are all decreased. There is a greater reduction of RBC count than hemoglobin or PCV.
2. MCV and MCH are increased, MCHC is normal. RDW is markedly increased.
3. Peripheral blood smear (figure 3) shows moderate to severe anemia with marked anisocytosis, poikilocytosis and macrocytosis (RBC are >9μm in diameter). The red cells are normochromic. Nucleated RBC with megaloblastic change, Howell Jolly bodies, Cabot rings and basophilic stippling are seen. Neutrophils appear larger than normal (macropolycytes) and nuclei have 5 or more lobes (hypersegmentation). There may be variable thrombocytopenia.
4. WBC may be normal in number or may show leucopenia.
5. Platelet count may be normal or decreased.
6. Reticulocyte count is decreased.

### 17.7.2 Bone Marrow

Bone marrow is hypercellular and shows erythroid hyperplasia. The red cell precursors are large with nuclei showing opened up chromatin which appears like a fine lattice or sieve like. The cytoplasm of the late erythroid precursors appears mature but the nucleus appears immature. This is called **Megaloblastic Maturation**. The myeloid precursors show giant metamyelocytes and band



forms. Megakaryocytes are normal or decreased in number. The nuclei however show hyperlobulation and fragmentation.

### 17.7.3 Biochemical Parameters

(a) Serum folic acid and red cell folate levels are decreased.

(b) Serum cobalamin levels are decreased.

(c) Two metabolites of the metabolic pathway of these vitamins namely serum homocysteine and methyl malonic acid levels may be increased.

(d) Schilling test: To confirm that the malabsorption of cobalamin is secondary to lack of intrinsic factor.

## 17.8 TREATMENT

The treatment consists of replacing the deficient vitamin and dietary advice. Response to treatment is seen as an increase in the reticulocyte count which starts about the second or third day. Increase in hemoglobin is seen by the end of a week of treatment. Treatment should be continued for at least six months to build up the stores in the body.

### Anemia in Chronic Liver Disease

In chronic liver disease there is anemia often associated with a mild degree of macrocytosis and raised MCV (usually between 100 to 110 fl). Other features that are present in the blood film are target cells and acanthocytes. These abnormally shaped red cells occur due to the deranged lipids in the RBC membrane. In liver disease due to chronic alcoholism there may be true megaloblastic anemia secondary to folic acid deficiency.

## INTEXT QUESTIONS 17.1

1. Macrocytic anemias are characterized by ..... with normal ..... content
2. Megaloblastic anemia occurs because of deficiency of ..... and .....
3. Vitamin B12 is also called as .....
4. Minimum daily intake of folic acid is ...../day
5. Folic acid deficiency in pregnancy causes ..... in newborn baby

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## 17.9 MACROCYTIC ANEMIA IN MYELODYSPLASTIC SYNDROME (MDS)

MDS is a preleukemic condition where the normal hematopoiesis in bone marrow is disturbed leading to morphologic and proliferative changes in the precursor cells. The ineffective hematopoesis affects all three cell lines. The red cells are macrocytic and have a raised MCV. It is important to differentiate between MDS and megaloblastic anemia because MDS may progresses into acute leukemia.

## 17.10 APLASTIC ANEMIA

### 17.10.1 Definition

Aplastic anemia is a condition where there is a failure of the bone marrow to produce red cells, white cells and platelets resulting in a PANCYTOPENIA.

### 17.10.2 Etiology

The bone marrow failure may be:

(a) Congenital or inherited – called Fanconi anemia

(b) Secondary to drugs, toxins, chemical, radiation exposure, or post certain viral infections

(c) Idiopathic where the cause is unknown.

### 17.10.3 Clinical Features

The patient presents with symptoms of anemia (tiredness, breathlessness, pallor) because marrow is not producing red cells. He/she may also have repeated and severe infections because normal WBC production is impaired. The patient may also have bleeding symptoms because of thrombocytopenia.

### 17.10.4 Laboratory Diagnosis

#### 17.10.4.1 Complete Blood Counts

1. Hemoglobin, PCV, RBC count all reduced
2. MCV normal or increased, MCH normal, MCHC normal or mildly increased, RDW normal
3. WBC count show leukopenia with neutropenia.
4. Platelet count is decreased

5. Reticulocyte count is markedly decreased
6. Peripheral blood smear shows pancytopenia. The red cells are few in number, normochromic normocytic or macrocytic. There is no polychromasia. nRBC are not seen. There is leukopenia with neutropenia. The majority of WBC seen are mature lymphocytes. The platelets are reduced in number but have normal morphology.

### 17.10.4.2 Bone Marrow Examination

Both bone marrow aspirate and trephine biopsy should be done because it is easier to assess bone marrow cellularity in the biopsy. The bone marrow is markedly hypocellular (<25% for age). The particles are made up of fat and underlying supporting fibrous tissue. The aspirate smears are poorly cellular and show marked decrease in erythroid and myeloid precursors and absent or occasional megakaryocytes. Most of the nucleated cells seen are lymphocytes and plasma cells. Tissue basophils and mast cells are increased. Iron stain shows adequate iron stores.

### 17.10.4.3 Treatment

Supportive treatment with blood transfusions, antibiotics and platelet transfusion is given Definitive treatment is immunosuppression or bone marrow transplantation.

Macrocytosis is also seen in neonatal blood, hypothyroidism and when there is polychromasia

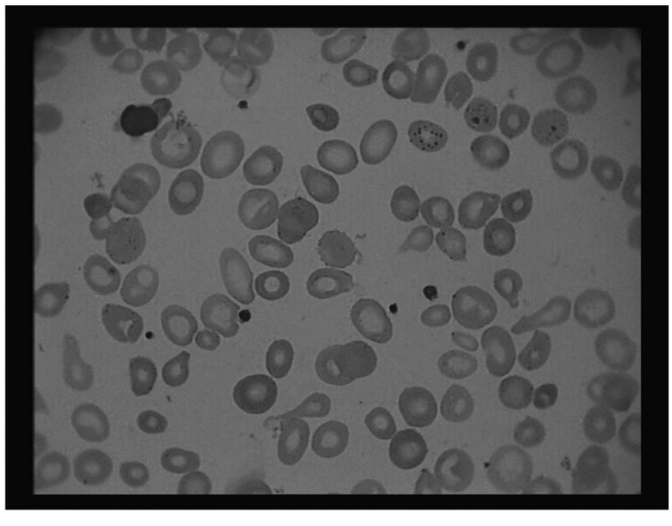

**Fig. 17.1:** Megaloblastic anemia

## INTEXT QUESTIONS 17.2

Match the following

| | |
|---|---|
| 1. Vitamin B12 | (a) Neural tube defects |
| 2. Parietal cells | (b) RBC diameter > 9 μm |
| 3. Folic acid deficiency | (c) Extrinsic Factor |
| 4. Macrocytes | (d) Pancytopenia |
| 5. Aplastic anemia | (e) Intrinsic Factor |

## WHAT HAVE YOU LEARNT

- Macrocytic anemias are characterized by presence of microcytes (RBC >9 μm in diameter) with normal haemoglobin content
- In macrocytic anemia, MCV and MCH is increased and MCHC is normal
- Megaloblastic anemia occurs due to deficiency of vitamin B12 or cobalamin and folic acid
- Vitamin B12 is synthesized only by microorganisms and a strict vegetarian diet is deficient in this vitamin
- Vitamin B12 is called Extrinsic factor and Parietal cells is called Intrinsic factor
- Cobalamin is transported in plasma by TC II – cobalamin complex
- Dietary insufficiency because of pure vegetarian diet, lactation & inability to absorb vitamin following gastric surgery, lack of hydrochloric acid caused vitamin B12 deficiency
- Folic acid is absorbed in small intestine mainly the jejunum
- Bone marrow in folic acid deficiency is hypercellular with erythroid hyperplasic
- The cytoplasm of the late erythroid precusors appears mature but nucleus appear immature and is called Megaloblastic maturation and Myeloid precursors show giant metamyelocytes and band forms
- Serum folic acid, red cell folate and Serum cobalamin levels are decreased
- Aplastic anemia results in pancytopenia
- In bone marrow examination, the smears are hypocellular and show marked decrease in erythroid and myeloid precursors and absent megakaryocytes.

## TERMINAL QUESTIONS

1. Define megaloblastic anemia
2. Describe the blood and bone marrow findings in megaloblastic anemia.
3. Give the normal values for the following:-
   (a) serum cobalamin .....
   (b) serum folate .....
   (c) red cell folate .....
   (d) MCV .....
4. Name 4 conditions where red cells are macrocytic.
   (a) .....
   (b) .....
   (c) .....
   (d) .....

## ANSWERS TO INTEXT QUESTIONS

### 17.1

1. Macrocytes, haemoglobin
2. Vitamin B 12 & Folic acid
3. Extrinsic factor
4. 50 µg
5. Neural tube defects

### 17.2

1. (c)
2. (e)
3. (a)
4. (b)
5. (d)