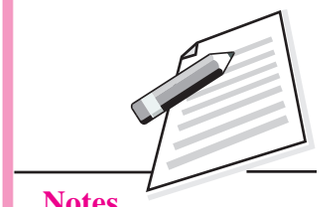


Notes

16

MICROCYTIC HYPOCHROMIC ANEMIA

16.1 INTRODUCTION

Microcytic hypochromic anemia is characterized by decreased haemoglobin, Packed Cell Volume (PCV), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC) and normal to increased Red Cell Distribution Width (RDW). RBC count is normal to increased depending upon the cause of anemia. The peripheral blood smear shows red cells which are smaller in size (microcytes) containing less haemoglobin (hypochromic).

OBJECTIVES

After reading this lesson, you will be able to:

- describe the basics of normal iron metabolism
- explain the biochemical parameters to measure iron in the body
- describe the causes of iron deficiency anemia
- discuss the laboratory diagnosis of iron deficiency anemia
- explain the differential diagnosis of hypochromic microcytic anemia

16.2 DEFINITION

Microcytic hypochromic anemia is characterized by decreased hemoglobin, PCV, MCV, MCH, MCHC and normal to increased RDW. RBC count is normal to increased depending upon the cause of anemia. The peripheral blood smear shows red cells which are smaller in size (microcytes) containing less hemoglobin (hypochromic).

Examples

Iron deficiency anemia

Anemia of chronic disorders

Disorders of globin synthesis

(eg. Thalassemia minor)

Sideroblastic anemias

Lead intoxication

16.3 IRON DEFICIENCY ANEMIA

16.3.1 Incidence

This is the most common type of anemia found worldwide and in India. It is seen in all age groups but is more common in women of the child bearing age and in children.

16.3.2 Cause

The anemia is caused by the deficiency of iron which is essential for the formation of normal hemoglobin.

16.3.3 Iron Metabolism

A basic understanding of iron metabolism is essential to understand the pathogenesis of iron deficiency anemia

16.3.3.1 Distribution of Iron in the Body

A. Hemoglobin – the major component of iron (60%) in the body is in the erythron (RBC + developing erythroid cells in bone marrow) 1 ml of RBC contains approximately 1 mg of iron

B. Myoglobin – Iron is also present in muscle tissue.

C. Enzymes – trace amounts of iron are present in certain enzymes in cells like cytochromes, catalases, peroxidases

D. Storage iron. Iron is recycled when RBC break down and is utilized for new hemoglobin synthesis. Iron is stored as

(a) Ferritin. The iron in macrophages is bound to a protein called apoferritin and is stored as ferritin.

(b) Haemosiderin – is another form of storage iron in macrophages.

16.3.3.2 Iron Intake

Iron is present in food as haeme iron and as non haeme iron. An average diet contains 10 – 15mg/day. Only 5 – 10% (~3.5mg/day) is absorbed from the food. Foods containing iron are meat, fish, eggs, liver, dhals, dried fruits, spinach.

16.3.3.3 Iron Requirements

Males 1mg/day Females 1.5mg/day Pregnancy and lactation 2mg/day

16.3.3.4 Iron Absorption

Iron absorption is an active process and requires ion transporters and enzymes which control the amount of iron absorbed. It is absorbed in the proximal small intestine at the brush border of the lining epithelium, close to the gastric outlet. In the stomach the gastric juices free the heme from its bound form and provide an acidic pH. The pathways for absorption are different for heme and non heme iron (Fe3+). The ferric (Fe3+) nonheme iron must first be converted into ferrous (Fe2+) form so that it can be transported across the membrane via a transporter (divalent metal ion transporter; DMT1). Heme iron is directly moved across the apical membranes through other transporters. Once inside the cell both types of iron have similar fate. Depending upon the body requirements, the absorbed iron is either retained in the mucosal cell or is transferred into plasma.

16.3.3.5 Iron Transport

Iron combines with a plasma protein called transferrin for transport in plasma. It is usually 30% saturated with iron so the serum iron is 100 µg/dL in females and 120 µg/dL in males. The normal percentage saturation of transferrin is 35 ±15%. The transferrin iron complex is attached to the transferrin receptors on the surface of macrophages and internalized. The iron is stored in macrophages in the marrow until required by the developing RBC to make haemoglobin. The transferrin returns to plasma

16.3.3.6 Iron Loss

Iron is lost from the body through shedding of skin and mucosal epithelial cells. Women lose iron during menstruation, in pregnancy and lactation

Iron Deficiency Anemia

16.3.4 Causes of iron deficiency

Iron deficiency occurs due to (a) decreased iron intake, (b) decreased absorption, (c) chronic blood loss or (d) increased requirement.

Notes

(a) **Decreased iron intake** – infants, elderly, poor dietary intake, decreased stores in babies born to iron deficient mothers.

(b) **Decreased absorption** – diseases of the stomach and duodenum and malabsorption.

(c) **Increased loss** – chronic blood loss due to gastro intestinal bleeding, hook worm infestation, excessive periods, multiple and frequent pregnancy etc.

(d) **Increased requirements** – Growing infants, children, adolescents and pregnant women.

16.3.4.1 Clinical presentation

Patients may be asymptomatic or present with fatigue, poor performance status, have difficulty in swallowing and in severe cases may have breathlessness. Some patients especially children may eat mud (pica). Patients have pallor, thin hair, ulcers in the angle of the mouth (angular stomatitis), bald tongue, flat and sometimes spoon shaped nails (koilonychia). There may be pedal edema and cardiac enlargement in severe anemia.

Stages in development of iron deficiency

Iron deficiency develops in a sequential manner and may be classified into 3 stages:

(a) Prelatent: Decreased storage iron without decrease in serum iron levels

(b) Latent: Exhausted iron stores with limited decrease in serum iron levels, the patients are still not anemic

(c) Anemia: Hemoglobin concentration falls and iron deficiency anemia is symptomatic.

16.3.4.2 Laboratory diagnosis

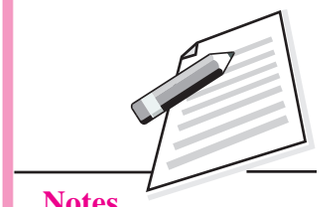
16.3.4.2.1 Complete blood counts

(a) Hemoglobin, PCV and RBC count are decreased. Anemia is commonly around 6 0 -7g/dl.

(b) MCV, MCH and MCHC are all decreased. The RDW is increased ~17 – 23%

(c) WBC count is normal.

(d) Platelet count may be normal or may show thrombocytosis.



16.3.4.2 Peripheral blood smear (PBS)

The peripheral blood smear (Fig. 16.2) shows variable morphology depending on the degree of iron deficiency. RBCs display variable degrees of anisocytosis (variation in size of RBC), microcytosis (RBC size <6.0µm diameter), hypochromia (increase in central pallor) and poikilocytosis (variation in shape). WBC morphology is normal Eosinophilia may be present in hook worm infestation. Thrombocytosis is frequently encountered in iron deficiency anemia.

16.3.4.3 Biochemical tests

The following iron profile is seen in patients with iron deficiency anemia:

- Serum iron is decreased (normal: 60-170µg/dL)
- Total iron binding capacity (TIBC) is increased (normal: 250-400 µg/dL)
- Transferrin saturation is decreased (normal: 16-50%)
- Serum ferritin is decreased (normal: 15-300 µg/L in males and 15-200 µg/L in females)

16.3.4.4 Bone marrow examination

There is minimal utility of bone marrow examination in cases of iron deficiency anemia as the diagnosis is based in CBC, PBS and biochemical findings. The most characteristic feature is absent or severely reduced macrophage iron (storage iron) as evidenced by Prussian blue staining. There is mild to moderate erythroid hyperplasia. The normoblasts appear small, have scant cytoplasm and irregular ragged cytoplasmic borders. The myeloid precursors and megakaryocytes are normal.

16.3.5 Differential Diagnosis

Other microcytic hypochromic anemias – Anemia of chronic disease, disorders of globin synthesis (beta thalassemia minor), sideroblastic anemia and lead intoxication.

INTEXT QUESTIONS 16.1

1. In Hypochromic microcytic anemia, red cells are ..... in size and contain ..... amount of Haemoglobulin
2. 1ml of RBC contain ..... mg of Iron
3. Iron is stored as ..... & .....
4. Iron in macrophages is bound to a protein called as .....
5. Iron requirement in pregnancy & Lactation is ..... mg.day

6. Iron combines with plasma protein called .....
7. Spoon shaped nails is described as .....
8. Children eating mud is described as .....

16.4 ANEMIA OF CHRONIC DISEASE

16.4.1 Definition

Anemia of chronic disorders is a type of anemia associated with a variety of chronic inflammatory, infectious or neoplastic disorders. The anemia usually develops when the above mentioned diseases persist for more than 1 or 2 months. It is secondary to inability of developing erythroid cells to utilize the available iron.

16.4.2 Associated Conditions

This type of anemia is commonly seen in the general population as it is associated with many chronic disorders. It may be associated with infections like tuberculosis, osteomyelitis, endocarditis, chronic abscesses; connective tissue disorders like rheumatoid arthritis, systemic lupus erythematosus; carcinoma, lymphomas and alcoholic liver diseases.

16.4.3 Pathogenesis

The most important abnormalities which occur in anemia of chronic disorder are: decreased red cells survival, inadequate marrow response, impaired iron mobilization and iron uptake by erythroid cells. These abnormalities are thought to be the effect of cytokines that are released during inflammation.

16.4.4 Laboratory Diagnosis

(a) Hemoglobin is ~9.0 -10.0g/dl, PCV and RBC count are mildly decreased.

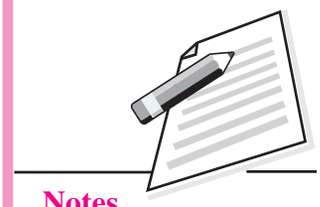
(b) The MCH is decreased, MCV may be normal or mildly decreased (MCV <72fl is rare), MCHC is normal, RDW is mildly increased.

(c) The peripheral blood smear show normocytic normochromic or microcytic hypochromic red cells. Changes in WBC and platelets will reflect the underlying disorder

(d) The reticulocyte count is decreased.

(e) The bone marrow examination shows normocellular marrow with normoblastic erythroid hyperplasia and normal myeloid and megakaryocytic maturation. The amount of hemosiderin within macrophages is increased.

(f) The Biochemical tests show decreased serum iron, decreased TIBC, decreased transferring saturation and increased or normal serum ferritin.



INTEXT QUESTIONS 16.2

1. Anemia of chronic disorders are due to the inability of cells to utilize .....
2. Infections which cause anemia are ....., ... & .....
3. Connective disorder which cause anemia are ..... & .....
4. ..... released during inflammation blocking the reuse of iron causing anemia

16.5 β THALASSEMIA MINOR

16.5.1 Definition

This is an inherited defect in haemoglobin synthesis where there is a decrease in globin chain synthesis. When the patient inherits two thalassemia genes, one from each parent, he/she develops a severe form of anemia called thalassemia major. A person who has one thalassemia gene has a mild hypochromic microcytic anemia which must be differentiated from iron deficiency anemia.

16.5.2 Laboratory Diagnosis

(a) Hemoglobin, PCV are mildly decreased. **RBC count is increased.**

(b) MCV, MCH are decreased but MCHC is normal or mildly decreased. RDW is only mildly increased ~14 – 15%

(c) Peripheral blood smear shows mild anemia, uniformly microcytic hypochromic red cells with no polychromasia. Target cells may be present. WBC and platelets are normal.

(d) Reticulocyte count is increased.

(e) Biochemical tests show normal serum iron, serum TIBC, transferrin saturation and ferritin.

(f) The diagnosis is made by performing hemoglobin analysis by HPLC (high performance liquid chromatography). Patients with beta thalassemia trait show the presence of raised HbA_2 in the range of 3.5 to 7.0%, HbF 1 to 3%; the rest being constituted by HbA.

Important

In the Indian population where the incidence of the beta thalassemia gene is 3-15% depending on the region, it is important to detect the thalassemia carrier

and offer genetic counseling and screening of the spouse to prevent the birth of children with beta thalassemia major.

16.6 SIDEROBLASTIC ANEMIA

16.6.1 Defintion

This is a refractory anemia with microcytic hypochromic red cells due to a defect in heme synthesis and the inability of mitochondria of developing red cells to incorporate iron into the heme molecule. It is characterized by the presence of ringed sideroblasts (erythroblast with perinuclear distribution of Prussian blue positive granules) in the bone marrow.

16.6.2 Types of Sideroblastic Anemia

A. Hereditary – usually seen in males, X linked inheritance, rarely autosomal.

B. Acquired

(a) Clonal: Associated with myelodysplastic syndrome

(b) Reversible: Drug induced (anti TB drugs, chloramphenicol), alcoholism

16.6.3 Pathogenesis

There is a defect in heme synthesis and iron is not incorporated into heme in the mitochondria. The iron transported to the mitochondria gets accumulated and can be demonstrated by the presence of stainable iron in the form of a ring around the nuclei of erythroblasts in the marrow. These granules contain iron inside mitochondria. The insufficient heme synthesis may also be secondary to enzyme defects in heme biosynthetic pathways. Since heme synthesis is affected, the red cells contain less haemoglobin and a microcytic hypochromic anemia results.

16.6.4 Laboratory Diagnosis

(a) The degree of anemia is highly variable

(b) MCV may be markedly reduced in severe cases. MCH and MCHC are decreased. RDW is increased.

(c) WBC and platelets are usually normal

(d) Peripheral blood smear shows marked anisocytosis and poikilocytosis with appearance of microcytes, normocytic normochromic and target cells

(e) Bone marrow shows erythroid hyperplasia increased iron stores with more than 15% ringed sideroblasts. The marrow also will have features of the underlying associated disorders if any.

(f) Serum iron is increased, TIBC decreased, Transferrin saturation is increased, serum ferritin is increased.

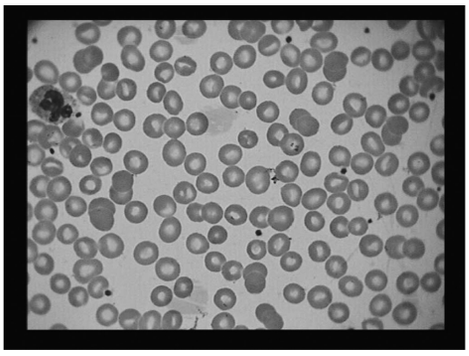


Fig. 16.1: Normal blood film

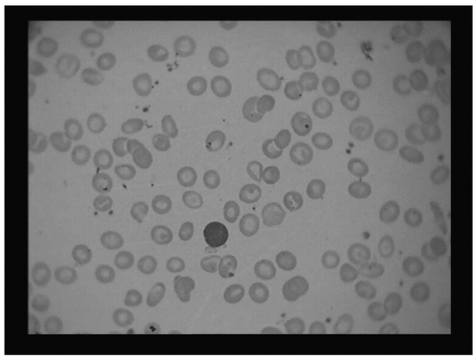


Fig. 16.2: Iron Deficiency anemia

INTEXT QUESTIONS 16.3

1. Thalasemia is caused because of decreased ..... synthesis
2. Diagnosis of Thalasemia is made by ..... test
3. Inability of red cells to incorporate iron into haeme molecule causes ..... anemia
4. In Sideroblastic anemia, RBC's may be ..... or .....

WHAT HAVE YOU LEARNT

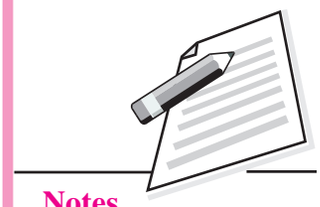
- Hypochromic microcytic anemias are characterized by decreased Hb, PCV, RBC, MCV, MCH, MCHC and increased RDW
- Blood film shows red cells smaller in size (microcytes), containing less hemoglobin (hypochromic)

Notes

- Iron deficiency anemia is caused by the deficiency of iron
- Iron is stored as Ferritin & Haemosiderin
- Iron requirement increases during pregnancy
- Iron combines with a plasma protein called Transferrin for transport in plasma
- In bone marrow absent or severly reduced macrophage iron (storage iron) is evidenced as by Prussian blu staining
- Serum iron is decreased with increased TIBC
- Transferrin saturation is reduced and serum Ferritin is reduced
- Chronic diseases like chronic inflammatory disorders and connective tissue diseases causes the erythroid cells unable to utilize the available irons
- Cytokines released during inflammation block the re use of iron
- Blood film shows anisocytosis, microcytosis & sometimes hypochromia
- Bone marrow shows normocellular marrow with normoblastic erythroid hyperplasia, delay in haemoglobinisation, normal iron store, and normal myeloid and megakaryocyte maturation
- Thalassemia minor is an inherited defect in haemoglobulin synthesis where there is globin chain synthesis
- Diagnosis of thalassemia is by High Performance Liquid Chromatography (HPLC)
- Defect in haeme synthesizes and inability of developing red cells to incorporate iron into haeme molecule causes sideroblastic anemia
- Sideroblastic anemia is X linked inheritance usually seen in males.

TERMINAL QUESTIONS

1. Name the cause of iron deficiency anemia
2. Describe the laboratory diagnosis of iron deficiency anemia.
3. Give the normal values for the following
   (a) Serum iron .....
   (b) Total iron binding capacity .....
   (c) Serum ferritin .....
   (d) Transferrin saturation .....



4. Define the following terms
   (a) Microcytosis .....
   (b) Hypochromia .....
   (c) Sideroblasts .....
   (d) Thalassemia minor .....

ANSWERS TO INTEXT QUESTIONS

16.1

1. Smaller & Less
2. 1 mg
3. Ferretin & Haemosiderin
4. Apoferritin
5. 2 mg
6. Transferrin
7. Koilonychia
8. Pica

16.2

1. Iron
2. Tuberculosis, Chronic abcesses & Osteomyelitis
3. Rheumatoid arthritis & Systemic Lupus Erythematosus
4. Cytokines

16.3

1. Globin chain
2. High Performance Liquid Chromatography (HPLC)
3. Sideroblastic
4. Normal or decreased