A REVIEW ON DIFFERENT TYPES OF ANAEMIA

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Abstract

Anaemia is a nutritional disorder accounting for 80 % of maternal deaths in India. It is classified based on morphology, etiology and pathophysiology. Iron deficiency anemia and vitamin B12 deficiency anemia are the most common types of anemia. Symptoms may include fatigue, skin pallor, shortness of breath, dizziness or palpitations. Vitamin B12 deficiency anaemia has symptoms such as tingling sensation in hands or feet, loss of sense of touch and dementia are observed. Anaemia caused by problems in bone marrow and stem cells such as Thalassemia or sickle cell anaemia tends to be more persistent and difficult to treat. Sideroblastic anaemia myelodysplastic anaemia are rare forms of anaemia. Iron therapy, Blood transfusion, Haemopoietic stem cell transplantation are mainstay of treatment for anaemia.

Key words: Iron deficiency anaemia, Thalassemia, Sideroblastic anaemia, Haemopoietic stem cell transplantation.

Introduction

Anaemia is a common nutritional disorder. Anaemia is defined as haemoglobin levels of less than 12g/dl in women and less than 13g/dl in men[1]. According to WHO one third of global population are anaemic. India contributes 80 % of maternal death due to anaemia [2]. RBC helps in carrying O_2 due to decreased RBC O_2 carrying capacity get decreased and has health implications that effects both morbidity and mortality. Anaemia impairs cognitive and psychomotor development in children[3]. Anaemia is a syndrome, not a disease and therefore aetiology must be investigated and therapy must be directed mainly to disease and not restoring of haemoglobin concentration[4].

Types[5]

Anaemia is classified based on morphology, aetiology and pathophysiology.

I. Morphology

i. Macrocytic anaemias

- Megaloblastic anaemia
- Vitamin B_{12} deficiency
- Folic acid deficiency anaemia

ii. Microcytic hypochromic anaemia

- Iron deficiency anaemia
- Sickle cell anaemia
- Thalassemia
- Genetic anomaly
- Other hemoglobinopathies (abnormal haemoglobins)

iii. Normocytic anaemias

- Recent blood loss
- Haemolysis
- Bone marrow failure
- Anaemia of chronic disease
- Renal failure
- Endocrine disorders

- Myelodysplastic anaemias

II. Aetiology

i. Deficiency of:

- Iron
- Vitamin B_{12}
- Folic acid
- Pyridoxine

ii. Central- caused by impaired bone marrow function:

- Anaemia of chronic disease
- Anaemia of the elderly
- Malignant bone marrow disorders

iii. Peripheral:

- Bleeding (haemorrhage)
- Haemolysis (haemolytic anaemias)

III. Pathophysiology

i. Excessive blood loss

- Recent haemorrhage
- Trauma
- Peptic ulcer

ii. Deficiency of erythroblast:

- Aplastic anaemia

MACROCYTIC ANEMIA

It is defined as the red blood cell Mean Corpuscular Volume (MCV) > 100 femoliter. Mean corpuscular volume is calculated by using red blood cell count, haemoglobin concentration and haematocrit[6].

MCV = haematocrit (%) x 10/RBC count (10^6/microlts)[6]

Megaloblastic anaemia

Megaloblastic anaemia is defined as a group of anaemias that are caused by abnormal DNA synthesis. It is identified by the irregular findings in the peripheral blood smear and bone marrow samples[7].

Aetiology: The two main causes of megaloblastic anaemia include deficiency of folic acid and vitamin B_{12}. These deficiencies result in impaired DNA synthesis and inadequate erythropoiesis. Because of the two reasons amount of unconjugated bilirubin and serum lactate dehydrogenases are increased[8]. Drugs that cause megaloblastic anaemia are chemotherapeutic agents like cyclophosphamide, methotrexate, azathioprine, hydroxyurea, mercaptopurine and antimicrobials like pyrimethamine, sulfamethoxazole, trimethoprim, acyclovir[9].

Symptoms: Symptoms of megaloblastic anaemia include pallor, fatigue, jaundice, weight loss, fever, skin hyperpigmentation and enlargement of liver and spleen[10]. Oral symptoms include glossitis, oral ulcers, angular cheilitis, oral candidiasis, erythematous mucositis[11]. Neurological symptoms like memory loss, dementia, loss of coordination, urinary and faecal incontinence, erectile dysfunction, muscle weakness and spasticity[12].

Diagnosis: Megaloblastic anaemia is diagnosed by peripheral blood smear showing large oval shaped red blood cells containing mean corpuscular volume greater than 115 fl and by doing complete blood picture and bone marrow aspiration[8].

Pharmacological management of megaloblastic anaemia[7]

Cyanocobalamin: 1000-2000 mcg/day PO or 1000 mcg/day IM for two weeks until blood levels normalize.

Folic acid: 1-5 mcg/ day PO for 3-4 months.

Vitamin B_{12} Deficiency anaemia

Vitamin B_{12} deficiency anaemia also called as pernicious anaemia is a condition in which body does not has enough healthy red blood cells due to lack of vitamin B_{12}. It is a common cause of megaloblastic anaemia. Vitamin B_{12} is essential for neurologic functions, red blood cell production and DNA synthesis[13].

Aetiology: Ubiquitous use of gastric acid blocking agents can lead to decreased vitamin B_{12} levels[14]. Most frequent cause of severe vitamin B_{12} deficiency is loss of intrinsic factor due to autoimmune atrophic gastritis, total or partial gastrectomy, gastric bypass surgery, inflammatory bowel disease, vegetarian diet, use of drugs like metformin[15].

Symptoms: Pallor, neuropathy, ataxia, degeneration of spinal cord, fatigue, jaundice, peripheral neuropathy, diarrhoea, glossitis, neuropsychiatric disturbances[16].

Diagnosis: Mean corpuscular volume (MCV) will get elevated, MCV increases before haemoglobin levels decrease.

Peripheral blood smear- presence of oval macrocytes suggests megaloblastic disorder.

Serum cobalamin measurement- lower limit of normal serum cobalamin is 200 pg/ml[17].

Treatment: Treatment of vitamin B_{12} deficiency involves repletion with B_{12}. Duration and route of treatment depends on aetiology of deficiency.

If aetiology is strict vegetarian diet oral supplement of B_{12} is adequate[16].

If aetiology is gastric bypass surgery, partial gastrectomy and inflammatory bowel disease – 1000 mcg IM cyanocobalamin daily or on alternate days for one week, then weekly once for 4-8 weeks and then monthly once for life time or oral cyanocobalamin at a daily dose of 1000-2000 mcg.

If aetiology is use of metformin and acid blocking agents- 1000 mcg IM cyanocobalamin daily or on alternate days for one week, then weekly once for 4-8 weeks and then monthly once for life time or oral cyanocobalamin at a daily dose of 500-1000 mcg[15].

Folic acid deficiency anaemia

Folate deficiency anaemia is lack of folic acid in the blood, folic is a B vitamin that helps body make red blood cells. Low level of folic acid causes megaloblastic anaemia[18].

Aetiology: Folic acid deficiency can arise from multiple causes including inadequate dietary intake. Heating during cooking destroys folic acid. Diseases such as celiac disease, topical sprue, short bowel syndrome, amyloidosis, gastric bypass or mesenteric vascular insufficiency inhibits folate absorption resulting in folate deficiency[19]. Drugs such as phenytoin, methotrexate and trimethoprim can also cause folate deficiency. Alcoholism, pregnancy, haemolytic anaemia and dialysis can also result in folate deficiency[20].

Symptoms: Pale skin, decreased appetite, being irritable, lack of energy, diarrhoea, smooth and tender tongue [18].

Diagnosis: Decrease in haematocrit and haemoglobin levels, increase in mean corpuscular volume.

Serum folate levels less than 2 ng/dl are considered deficient[19].

Treatment: Folic acid supplements are efficacious for treatment of deficiency, in severe cases if oral therapy fails higher doses can be tried. In case of failure folic acid injections are given. It is essential to rule out vitamin B_{12} deficiency before administrating folic acid as they will cause deterioration of neurological manifestations[21].

MICROCYTIC HYPOCHROMIC ANEMIA

Microcytic hypochromic anaemia is defined as the reduced size of red blood cells and less red colour than that of normal red blood cells[22].

Iron deficiency anaemia

Iron deficiency anaemia is a condition in which there is inadequate iron supplementation to maintain normal physiological functions[23]. Iron is a vital element in the transporting of oxygen in haemoglobin. Haemoglobin carries oxygen from lungs to different parts of the body[24]. The normal daily intake of iron for an adult is 10 to 15 mg in which 1-2 mg is absorbed by duodenal enterocytes. This absorbed iron gets reduced to ferrous from ferric iron with the help of low gastric pH[25].

Aetiology: Causes of iron deficiency anaemia include:

1. Insufficient iron intake: Iron deficiency anaemia is a nutritional disorder caused due to deficiency of iron, folic acid, cyanocobalamin, ascorbic acid[24].

2. Abnormal iron loss: It occurs due to vaginal bleeding, uterine bleeding and gastrointestinal bleeding[26], frequent menstruation, less time gap between two blood donations, accidents, haemorrhage, surgery and intravascular haemolysis[24].

3. Increased iron requirement: It occurs during conditions like pregnancy and lactation[24].

4. Impaired iron absorption: Iron is available in two forms i.e., heme iron and non-heme iron. Heme iron is found in meat whereas non-heme iron is available in plant sources and dairy products[24].

Symptoms: Symptoms of iron deficiency anaemia include tachycardia, heart failure, cardiomegaly, anorexia, dysphagia, angular stomatitis, malaise, insomnia, learning difficulty, papilloedema [27].

Diagnosis: Iron deficiency anaemia is diagnosed based on less serum iron, low transferrin solution percent and by decreased ferritin levels [28]. It is also diagnosed by using complete blood count, peripheral blood smear, urea and creatinine levels, total iron binding capacity, transferrin saturation index [27].

Table 1: Diagnostic tests for Iron Deficiency Anaemia (IDA)[24]

S. No	Tests	Normal range	IDA
1.	Total Iron Binding Capacity	240-450 mcg/dl	High
2.	Serum iron	Men: 55-160 mcg/dl Women: 40-155 mcg/dl	Low
3.	Transferrin saturation	Adults 20 %-50 % Children >16 %	<12-16 %
4.	Serum ferritin	Female: 15-200 ng/ml Male 20-300 ng/ml	<15 ng/l
5.	Haemoglobin	Men 130 g/l Women 120 g/l Pregnant women and school children 110 g/l	Low

Treatment

Iron deficiency anaemia can be treated by giving oral iron therapy, parentral iron therapy and blood transfusions.

Oral iron therapy: Daily requirement of iron in an adult is about 120 mg for three months and for children 3 mg/kg to 60 mg/kg per day [29]. The absorption rate of 100 mg oral iron is 20-25 %. Oral therapy is very effective and should be carefully monitored. The Hb levels will increase up to 2 g/l within a period of four to eight weeks [30].

Parentral iron therapy: It is used in patients with who cannot able to absorb oral iron.

Ex: patients who have undergone surgeries like gastrectomy, gastrojejunostomy [31].

IV drugs-

Sodium ferric gluconate- 12.5 mg/ml

Iron dextran- 50 mg/ml

Iron sucrose- 20 mg/ml

Ferumoxytol- 30 mg/ml

Oral drugs-

Ferrous fumarate- 325 mg tablet, it contains 106 mg of elemental iron, it should be taken two times a day.

Ferrous gluconate- 300 mg tablet, it contains 38 mg of elemental iron to be taken twice or thrice a day.

Ferrous sulfate- 325 mg tablet, it contains 65 mg of elemental iron, it should be taken thrice a day[29].

Sickle cell anaemia

Sickle cell anaemia is a hereditary disorder caused due to point mutation in the beta globin gene results in the substitution of valine instead of glutamic acid in the beta globin chain [32]. Sickle cell anaemia is a lifelong hematologic disorder identified by abnormal, irregular, sickle shape of red blood cells[33].

Aetiology: Sickle cell disease have a different form of haemoglobin. Patients with the most common variant of sickle cell disease have haemoglobin S (Hb S). Normal haemoglobin is usually designated Hb A. Hb (S) has valine instead of glutamic acid as the sixth amino acid in the beta polypeptide when compared to normal haemoglobin. People with homozygous haemoglobin S develops many problems which includes anaemia [34].

Symptoms: Fatigue, shortness of breath, dizziness, headache, coldness in the hands and feet, pale skin and chest pain [2]. Orofacial pain, paraesthesia of mental nerve, pulpal necrosis, enamel hypo- mineralisation, acute facial swelling, gingival enlargement [35].

Diagnosis: Haemoglobin electrophoresis, High Performance Liquid Chromatography and iso-electric focusing are used to determine the presence of abnormal haemoglobins [36]. Sickle solubility test is also used to determine sickle haemoglobin. The diagnosis of sickle cell anaemia can be confirmed by high performance liquid chromatography [33].

Treatment: Hydroxyurea also known as hydroxycarbamide is used as first line therapy or drug of choice for sickle cell disease and is approved by Food and Drug Administration. Agent which prevent dehydration of sickle red cell include Voxelotor (anti sickling agent) of 900 mg/d up to 1500 mg/d for 24 weeks.

Agents interfering with red cell vascular adhesion are:

Regadenoson, a selective A2A adenosine receptor antagonist.

Antibodies against iNKT cells and omega-3 fatty acids.

Antioxidant agents like N-Acetyl-Cysteine and L-Glutamine of 0.3 g/kg twice a day [37].

Long Term Blood Transfusion

Long term blood transfusion is used to maintain a normal Hb S percentage. The main complication associated with this blood transfusion is alloimmunization of antigens which is common in sickle cell disease patients.

Haemopoietic Stem Cell Transplantation

Haemopoietic stem cell transplantation is also used in the treatment of sickle cell anaemia [38]. Pluripotent stem cell is responsible for the generation of new red blood cells. Depending on the donor haemopoietic stem cell transplantation is classified in to allogenic, autogenic and syngenic [39].

Thalassemia

Thalassemia is one of the genetic disorders, occurs due to the abnormal form of haemoglobin and results in destruction of red blood cells which results in anaemia [40].

Thalassemia is of two types, based on the type of globin chain in haemoglobin is insufficiently produced [41]. They are:

1. Alpha thalassemia 2. Beta thalassemia.

Alpha thalassemia: It occurs through inadequacy in the production of alpha globin chain in the haemoglobin. It is also known as Hydrop's Foetalis [42].

Beta thalassemia: Beta thalassemia occurs due to the reduced synthesis of beta subunit in the haemoglobin [43].

Symptoms: Anorexia, jaundice, enlargement of liver and spleen and bone problems like osteoporosis. Facial features like brodie syndrome, chipmunk faces, pneumatisation of paranasal sinuses and Oral manifestations like mucosal pallor, atrophic glossitis, severe gingivitis, inflammation of salivary glands [44].

Diagnosis: Thalassemia is diagnosed by using: complete blood count, High Performance Liquid Chromatography, electrophoresis.

Complete Blood Count: For a positive result mean corpuscular volume should be of less than 80 fl and mean corpuscular haemoglobin value should be less than 27 pg [45].

High performance Liquid Chromatography: It is used as a diagnostic test for identifying thalassemia because of its speed and reliability. It is a sensitive method for the identification of Hb A_2. It uses double wave length detection [46].

Electrophoresis: Haemoglobin analysis was performed with the help of capillary electrophoresis. DNA extraction and detection of beta globin is done by blood extraction method [47].

Treatment: Iron chelators: There are three iron chelators deferoxamine, deferiprone and deferasirox.

Table 2: Treatment of Thalassemia [48]

S.No	Agent	Route and half life	Classification	Dosage regimen	Adverse effects
1.	Deferoxamine	Iv or SC $T_{1/2}$-8 to 10 min	Hexadentate	30-40 mg/kg/day over 8-12 h 5-7 day/week	Anaphylaxis, local irritation, retinopathy, hearing loss
2.	Deferiprone	Oral 12-18 hrs	Tridentate	20-40 mg/kg/day once daily	Diarrhea, rash, proteinuria, hepatic and renal dysfunction
3.	Deferasirox	Oral 1.5-4 hrs	Bidentate	75-100 mg/kg/day 3 divided doses daily	Arthralgia, arthropathy, agranulocytosis

Patients with beta thalassemia should receive blood transfusion for throughout their life time for every 2-5 weeks depending on the individual to maintain haemoglobin level up to 9-10.5 g/d [49].

NORMOCYTIC ANEMIA

Normocytic anaemia is defined as decrease in circulating red blood cell mass. In normocytic anaemia the mean corpuscular volume is within normal range but haemoglobin and haematocrit are decreased[50].

Aetiology: Normocytic anaemia can be congenital or acquired. Congenital cause of normocytic anaemia is breaking up of red blood cells. Acquired form of normocytic anaemia is long term disease observed in diseases such as kidney failure, cancer, rheumatoid arthritis, thyroiditis, acute blood loss, pregnancy, over hydration and some endocrine disorders[51].

Symptoms: Normocytic anaemia is often asymptomatic and is often coincidentally stumbled upon screening laboratory testing[52].

Diagnosis: Normocytic anaemia is usually diagnosed by complete blood count.

A normocytic anaemia with normal reticulocyte and normal red blood cell distribution width count is usually related to chronic disease. However, an elevated reticulocyte count suggest that cause of anaemia is bleeding or haemolysis. Additional diagnostic tests include serum creatinine, blood urea nitrogen for patients with chronic kidney disease. International Normalised Ratio (INR) and liver function tests for patient with liver disease and urine human chorionic gonadotropin if pregnancy is suspected[53].

Treatment: Goal of treatment should include treatment of underlying condition and correcting reversible cause of anaemia. Red blood cell transfusions are effective but should be limited to situation in which oxygen transport is inadequate. Erythropoietic agents (recombinant epoetin α and recombinant darbepoetin α) are used to stimulate erythropoiesis. Dose of epoetin α: 50-100 U/Kg three times per week. Dose can be increased to 150 U/kg if there is no increase in haemoglobin concentration after 6-8 weeks. Iron deficiency can occur in patients treated with epoetin so close monitoring of iron levels is necessary[5].

Diet: Patient should take balanced diet and replenish body with deficiency element. Vitamin B12 can be obtained from meat, fish, eggs, and milk, cereals, soy milk and yeast extract. Iron is found in Liver, meat, green vegetables like spinach, kale, collard greens, dandelion greens, enriched flour, eggs and milk, sea foods like shell fish, sardines, fresh salmon, fresh tuna, fortified pasta, fortified white rice, peas, cashews, sunflower seeds, almonds. Folic acid is found in green vegetables especially broccoli and spinach, citrus fruits, beans, whole grains. Iron tablets should be taken with vitamin C rich foods such as tomatoes, strawberries, orange juice and red peppers, beets for ease of absorption. Eating an overall healthy diet rich in dark, leafy greens, nuts and seeds, seafood, meat and beans can help manage anaemia.

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