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ANEMIA

- Anemia is defined as the reduction of the red blood cells (RBC^S) volume or the hemoglobin (Hb) concentration below the range of values occurring in healthy persons.
- Normal Hb & hematocrit (PCV) vary substantially with age & sex. There are also racial differences, with significantly lower Hb levels in African American children than in white non-Hispanic children of comparable age.
- ↓ Hb → ↓ O2 carrying capacity of the RBC.

Physiological response to anemia

- ↑ cardiac output.
- Shunting of the blood flow towards vital organs & tissues.
- ↑ 2,3-DPG (diphosphoglycerate) in RBC (shift to the right of O2 dissociation curve) → ↓ affinity of Hb to O2 →↑ transfer of O2 to the tissues (this also occurs in high altitude).
- ↑ Erythropoietin (EPO) & consequent ↑ RBC^S production by the bone marrow further assist the body to adapt.

Normal values

- Normal RBC^S count is about 4×10^6 / mm^3.
- Normal absolute reticulocyte count is about 40,000 / mm^3.
- Normal reticulocyte % is about 1%.
- Normal Hb level: Cord blood:Mean:16.8 g/dl, Range:13.7-20.1 g/dl, at 2 wk: 16.5(13-20), at 3 mo: 12(9.5-14.5), at 6 mo to 6 yr: 12(10.5-14), at 7-12 yr: 13(11-16), Adult: female: 14(12-16), male: 16(14-18)

Approach to common causes of anemia in children

- A detailed history & thorough physical examination are essential. Important historical facts should include age, sex, race & ethnicity, diet, medications, chronic diseases, infections, travel & exposure. A family history of anemia & associated difficulties (as splenomegaly, jaundice, early-age onset of gallstones) is also important.
- Clinical features generally do not become apparent until Hb level falls below 7-8 g/dL.
- Anemia may be morphologically categorized on the basis of RBC size (MCV) & microscopic appearance to:

1. Microcytic anemia:

A. Low/Inadequate reticulocyte count: IDA, Thalassemia trait, Chronic disease/inflammation, Lead poisoning, Sideroblastic anemias, Copper deficiency, IRIDA.
B. High reticulocyte count: Thalassemia syndromes, Hb C & E disorders, Pyropoikilocytosis.

2. Normocytic anemia:

A. Low/Inadequate reticulocyte count: Chronic disease/inflammation, RBC aplasia (TEC, Infection, Drugs), Malignancy, Endocrinopathies, Renal failure, Acute bleeding, Hypersplenism, Dyserythropoietic anemia II, Hemophagocytic syndrome.

B. High reticulocyte count: Antibody mediated hemolysis, Hypersplenism, Microangiopathy (HUS, TTP, DIC, Kasabach-Merritt), Membranopathies (spherocytosis, elliptocytosis, ovalocytosis), Enzymopathies (G6PD, PK deficiencies), Hemoglobinopathies (HBSS, SC).

3. Macrocytic anemia:

A. Low/Inadequate reticulocyte count: Folate deficiency, Vitamin B12 deficiency, Acquired aplastic anemia, Congenital aplastic anemia (Diamond-Blackfan, Fanconi anemia, Pearson syndrome), Drug induced, Trisomy 21, Hypothyroidism, Oroticaciduria, Liver disease, Thiamine responsive anemia, Myelodysplasias.

B. High reticulocyte count: Dyserythropoietic anemia I , III & Active hemolysis with very elevated reticulocyte count.

Iron Deficiency Anemia (IDA)

- It is the most widespread & common nutritional disorder in the world. It is estimated that 30% of the global population suffers from IDA, & most of them live in developing countries. In the USA, 8-14% of children ages 12-36 mo are iron deficient, & 30% of them will develop IDA.
- The body content of iron is about 0.5 g in newborn & about 5 g in adult. About 1 mg of iron must be absorbed by GIT each day. Because of the absorption of the dietary iron in the proximal small intestine is about 10% of the eaten amount, a diet containing 8-10 mg of iron is required daily.
- During infancy, when growth is more rapid, the 1 mg/L of iron in cows & breast milk make it difficult to maintain body iron. Breastfed infants have an advantage, because they absorb iron 2-3 times more efficiently than infants fed cow's milk; nonetheless, breastfed infants are at risk of developing iron deficiency without regular intake of iron-fortified food by 6 months of age.

Etiology

1. Low birth-weight & unusual perinatal hemorrhage & early clamping of umbilical cord.
2. Dietary deficiency: Undernutrition is usually responsible for iron deficiency. Causes include failure of breast feeding, delayed or improper weaning, ingestion of large amount of cows milk, ingestion of little amount of iron-rich diet as iron-fortified milk, meat, green vegetables etc.

- In term, IDA due to dietary loss is unusual < 6 months of age & usually occurs at 9-24 months of age (the incidence ↓ after that).
- The usual dietary pattern in infants & toddlers with nutritional IDA in developed countries is excessive consumption of cow's milk (low iron content & blood loss from milk protein colitis) in a child who is often overweight or bottle feeding 12 month of age & of food not supplemented with iron.

3. Blood loss: particularly in older children & adolescents as menstrual losses, recurrent nosebleeds, intravascular hemolysis (malaria).

- Chronic IDA from occult bleeding as in peptic ulcer, mackle's diverticulum, intestinal polyps or hemangiomas, inflammatory bowel diseases(IBD), cow's milk allergy (blood loss can be prevented either by breastfeeding or delaying the introduction of cow's milk in the 1st year of life & then limiting the quantity to less than 24 oz daily), chronic diarrhea & rarely pulmonary hemsiderosis.
- In developing countries, infections with hookworm in, *Trichuris trichiura*, plasmodium, often contribute to ID.

4- Gastric bypass procedures or *Helicobacter pylori* infection, celiac disease or giardiasis may interfere with iron absorption.
5- Adolescents are also susceptible to iron deficiency because of ↑ requirements due to growth spurt, dietary deficiency, & menstrual blood loss (about 2% of adolescent girls have IDA). The highest risk of IDA (more than 30%) is among pregnant teenagers.

Clinical manifestations

- Most children with iron deficiency are asymptomatic & are identified by routine laboratory screening at 9-12 months of age.
- Pallor is the most important sign of IDA but is not usually visible until the Hb falls to 7-8 g/dL (pallor of the palms, palmar creases, nail beds, or conjunctivae).
- Older children may report cold intolerance, fatigue, exercise-induced dyspnea, or decreased mental acuity.
- In mild to moderate IDA (Hb: 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-DPG & a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted.
- When Hb level falls to <5 g/Dl, irritability, anorexia & lethargy develop, & systolic flow murmurs are often heard. As Hb continues to fall, tachycardia & high output cardiac failure can occur.
- Iron deficiency has non-hematologic systemic effects. Both ID & IDA are associated with impaired neurocognitive function in infancy. IDA is also associated with later, possibly irreversible, cognitive defects. Some studies suggest an increased risk of seizures, strokes, breath-holding spells in children.
- Pica, the desire to ingest non-nutritive substances (can result in ingestion of lead-containing substances leading to plumbism) & pagophagia, the desire to ingest ice, are other symptoms of IDA.
- IDA may lead to decreased cell mediated immunity & impaired neutrophil activity.

Laboratory findings

In progressive IDA, a sequence of biochemical & hematological events occur as follows :
- Depletion of tissue iron stores (↓ serum ferritin) then :
- ↓ serum iron, ↑ serum total iron binding capacity (TIBC or serum transferrin), & ↓ transferrin saturation then:
- ↑ free erythrocyte protoporphyrin (impaired Hb synthesis, ID→IDA) then ↑ RDW (variable sizes of RBCs), ↓ MCV, ↓ MCH (hypochromic microcytic RBC^S) then:
- RBC count decreases. The reticulocyte % may be normal or moderately ↑ , but absolute reticulocyte count shows insufficient response to the degree of anemia.
- Elliptocyte or cigar-shaped RBC are often seen. Detection of ↑ soluble transferrin receptor & ↓ reticulocyte hemoglobin concentration provide very useful & early indicators of ID, but availability of these tests is more limited. Bone marrow iron staining is the most accurate method of diagnosing IDA but is invasive, expensive & usually unnecessary.
- WBC count is normal, but thrombocytosis is often present. Thrombocytopenia is occasionally seen confusing the diagnosis with bone marrow failure disorders. Occult blood in stool may be seen. In most instances, a CBC demonstrating a microcytic anemia with ↑RDW, ↓RBC count, normal WBC count, & normal or ↑platelet count is sufficient for a presumptive diagnosis.
- Other laboratory studies as ↓ serum ferritin, ↓ serum iron & ↑ TIBC, are not usually necessary for diagnosis unless severe anemia requires more rapid diagnosis, other complicating clinical

factors are present, or the anemia does not respond to iron therapy. An increase in Hb ≥1 g/dl after 1 month of iron therapy is the most practical means of diagnosis.

Differential diagnosis

1. β-thalassemia & α-thalassemia : There are ↓ Hb & MCV, normal serum ferritin, TIBC, transferrin saturation, FEP, soluble transferrin receptor & reticulocyte Hb concentration, normal or ↑ RBC count & normal or minimally ↑ RDW.
2. Hemoglubinopathies as Hb E, & Hb C disease.
3. Anemia of chronic diseases & inflammation: It is usually normocytic anemia but can be microcytic in a minority of cases. There are ↓ Hb, TIBC & transferrin saturation, normal soluble transferrin receptor, normal or ↓ MCV, RBC count & reticulocyte Hb concentration, normal or ↑ RDW, & normal soluble transferrin receptor.
4. Lead poisoning : can cause microcytic anemia, but more often the microcytic anemia is caused by ID resulting in pica & secondary lead intoxication. There are ↑ FEP (free erythrocyte protoporphyrin), course basophilic stippling of the RBC^S, & ↑ blood lead level.
5. Sideroblastic anemia : They are acquired or hereditary disorders of heme synthesis → dimorphic anemia (hypochromic microcytic & normal RBC^S) & mostly occur in adulthood.

- When anemia is identified solely by Hb or hematocrit, 60% of children in developed countries with anemia have an explanation other than IDA. Caution should be used in treating these patients with iron without the benefit of CBC with differential to exclude more serious diagnosis.

Prevention

- Iron deficiency is best prevented to avoid both its systemic manifestations & the anemia. Breast feeding should be encouraged, with the addition of supplemental iron at 4 months of age.
- Infants who are not breastfed should only receive iron fortified formula (12 mg of iron/L) for the first year, & thereafter cow's milk should be limited to <20-24 oz daily. This approach encourages the ingestion of foods richer in iron & prevents blood loss due to cow's milk-induced enteropathy.
- Routine screening for all children using Hb or Hematocrit is done at 12 mo of age or earlier, if at 4 mo of age the child is assessed to be at high risk for ID as recommended by the American Academy of Pediatrics (AAP). This screening will not detect ID without anemia. Children with identified risk factors for IDA should be screened with a CBC.

Treatment

- The regular response of IDA to adequate amount of iron is a critical diagnostic & therapeutic feature.
- **Oral administration of simple ferrous salts** (most often ferrous sulfate) provides inexpensive & effective therapy. There is no evidence that the addition of any trace metal, vitamin or other hematinic substance significantly increase the response to simple ferrous salts. Calcium & fiber may decrease the absorption of iron, but this can be overcome with the co-administration of vitamin C. Tea is a significant inhibitor of iron absorption. Aside from the unpleasant taste of iron, intolerance to oral iron is uncommon in young children. In contrast, older children & adolescents sometimes have GI complaint that may improve with lower dose of iron.
- A daily total dose of 3-6 mg/kg of elemental iron in 1-2 doses is adequate. The maximum dose is 150-200 mg of elemental iron daily (ferrous sulfate has 20% elemental iron & is ideally

given between meals with juice) for 2-3 months after blood values normalize to reestablish iron stores.

- **Parenteral iron preparation** are considered when malabsorption is present or when compliance is poor, because oral therapy is otherwise as effective, much less expensive & less toxic. When necessary, IV low-molecular-weight iron dextran (the only FDA approved), parenteral iron sucrose, ferric carboxymaltose & ferric gluconate are available. Iron therapy may increase the virulence of malaria & certain gram-negative bacteria, particularly in developing countries. Iron overdose is associated with *Yersenia* infection.
- **Dietary counseling** is usually necessary. Excessive intake of milk, particularly cow's milk, should be limited. Dietary iron should also be increased. Iron from heme sources is 10 times more bioavailable than iron from non-heme sources. Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron & menstrual control by hormone therapy.
- **Follow-up:** If the anemia is mild, the only additional study is to repeat the blood count 1 month after initiating therapy at which Hb has usually risen by at least 1-2 g/dl & has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of reticulocytosis usually within 48-96 hr of starting treatment. The Hb will then begin to increase 0.1-0.4 g/dL per day depending on the severity of the anemia.
- When the anemia respond poorly or not at all to iron therapy, there are multiple consideration like poor compliance (true intolerance of iron is uncommon), incorrect dose or medication, malabsorption (celiac disease, giardiasis, others), medications (antacids, proton pump inhibitors, histamine2 blocking agents, brans, tannins, phytates), ongoing blood loss (GIT, menstrual respiratory), concurrent infection or inflammatory disorder inhibiting the response to iron, concurrent vitamin B 12 or folate deficiency, lead or aluminum toxicity or diagnosis other than IDA as thalassemia, Hb C & E, anemia of chronic disease, lead poisoning, sickle thalassemia Hb SC disease.
- **Iron-refractory IDA (IRIDA):** rare, autosomal recessive disorder of systemic iron balance characterized by defects in both absorption & utilization of iron. IRIDA is refractory to oral iron therapy & only partially responsive to parenteral iron therapy.
- **Blood transfusion** is rarely necessary. It should only be used when congestive heart failure is eminent or if the anemia is severe with evidence of substantial ongoing blood loss. Unless there is active bleeding, transfusion must be given slowly to avoid precipitating or exacerbating CHF.

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