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Review Article

Benign Causes of Anemia: Diagnosis and Management

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Abstract

Anemia is the most common blood disorder. It has so many types and causes, some can be really challenging and greatly affect the lives of individuals, other types can be considered really benign with no symptoms and/or has no impact on life expectancy of their patients. Here we discuss the causes of benign anemia in children, their diagnosis and management. As it's important to identify and differentiate the benign causes that require only minimal or slight intervention from physicians and avoid the patients unnecessary medication or blood transfusion.

Keywords: *Anemia; Benign*

Introduction

Anemia is the most common blood disorder; According to the 2001 World health Organization (WHO) data, 30% of the children aged between 0 and 4 years and 48% of the children aged between 5 and 14 years are anemic in developing countries [1].

Anemia may be defined as a reduction in red blood cell (RBC) mass or blood hemoglobin concentration. A hemoglobin (Hb) concentration 2 SDs below the mean Hb concentration for a normal population of the same gender and age range, as defined by the World Health Organization, the United Nations Children's Fund, and United Nations University [2].

In practice, anemia most commonly is defined by reductions in one or both of the following:

- Hematocrit (HCT): The hematocrit is the fractional volume of a whole blood sample occupied by RBCs, expressed as a percentage. As an example, the normal HCT in a child age 6 to 12 years is approximately 40 percent.
- Hemoglobin (HGB): This is a measure of the concentration of the RBC pigment hemoglobin in whole blood, expressed as grams per 100 mL (dL) of whole blood. The normal value for HGB in a child age 6 to 12 years is approximately 13.5 g/dL (135 g/L).

Normal ranges for HGB and HCT vary substantially with age, race, and sex (Table 1) [3].

Age	HB (g/l)	RBCS (*1012/l)	Ht
Birth	149 - 237	3.7 - 6.5	0.47 - 0.75
2 weeks	134 - 198	3.9 - 5.9	0.41 - 0.65
4 weeks	94 - 130	3.1 - 4.3	0.28 - 0.42
4 - 6 months	114 - 141	3.9 - 5.5	0.31 - 0.41
6 months to 1 year	115 - 135	4.1 - 5.3	0.33 - 0.41
1 year to 6 years	115 - 135	3.9 - 5.3	0.34 - 0.40
6 years to 12 years	115 - 155	4.0 - 5.2	0.35 - 0.45
12 years to 18 years female	120 - 160	4.1 - 5.1	0.36 - 0.46
12 years to 18 years male	130 - 160	4.5 - 5.3	0.37 - 0.49

There are so many reasons for anemia and some can be really challenging in terms of diagnosis and management. The prognosis of anemia mainly depends on its cause and type so it's of utmost importance to differentiate between anemias and detect the benign types.

Benign types refer to types of anemia that can be completely treated with no effect on life expectancy, so the scope of this article would focus only on benign causes of anemias, some of which are actually physiological. And we discuss the most common causes, how to diagnose and how to manage.

Physiological anemia of the newborn

This is the commonest type of anemia in young infants from birth up to three months of age. As after birth the tissue oxygenation improves markedly in comparison with fetal levels, erythroproduction is significantly diminished as so hemoglobin level decreases. Peak occurs at6 to 9 weeks [4]. At the nadir of the physiologic anemia in full-term infants, hemoglobin levels may be as low as 9.5 to 10 Gm. per 100 ml. at 6 to 8 weeks of age, and in premature infants 6 to 7 Gm. per 100 ml at 3 to 7 weeks of age. Hemoglobin values of this degree should be considered non-pathologic and do not require special hematinic therapy or blood transfusion. Anemia of prematurity (AOP) is an exaggerated, pathologic response of the preterm infant to this transition. AOP spontaneously resolves in many premature infants within 3 - 6 months of birth.

Practical considerations and management

For example, a drop in hemoglobin from 16 Gin. per 100 ml at birth to 8 Gin. per 100 ml at 6 weeks of age is not to be unexpected for a 1.5 Kg. premature infant; however, it would be abnormal for a full-term infant. Thus the fall from 16 to 8 Gin. per 100 ml in a 1.5 Kg premature infant, if it occurred by 2 weeks instead of 6 weeks of age would likewise be abnormal [5].

To differentiate physiological anemia of newborn from pathological types:

- Consider the timing and level of hemoglobin nadir.
- The general condition of the child and irritability.
- The presence of hemolysis like jaundice and dark colored urine.

Treatment

As a developmental process, physiologic anemia usually requires no therapy other than ensuring that the diet of the infant contains the essential nutrients for normal hematopoiesis, especially folic acid and iron. A premature infant who is feeding well and growing normally rarely needs transfusion unless there has been significant iatrogenic blood loss. Assessment of the overall clinical condition, including growth rate, and monitoring of hematocrit are good guides to transfusion of red cells.

Iron deficiency anemia (IDA)

This is the commonest cause of anemia worldwide. It can occur due to dietary causes or non-dietary causes. IDA is readily preventable, even in a profoundly socially disadvantaged population, by the provision of an iron supplemented formula in place of unmodified cows' milk.

Iron requirements

In the normal term infant, total body iron changes little during the first four months of life. Even though blood volume increases, total haemoglobin iron increases only slightly, as haemoglobin concentration falls during this period. Consequently, IDA in this age group is uncommon, except in the presence of gastrointestinal blood loss. The need for iron supplementation in the first few months is therefore questionable.

By 4 months of age, neonatal iron stores have been reduced by half, and exogenous iron is required to maintain haemoglobin concentration during the rapid phase of growth between 4 and 12 months. Absorption of about 0.8 mg or iron per day from the diet is required,

of which 0.6 mg is needed for growth, and 0.2 mg to replace losses. The reference nutrient intake for iron (mg/day) is 4.3 (4 - 6 months) and 7.8 (7 - 12 months) [6].

Iron absorption and losses

Iron in breast milk is present in low concentrations (0.06 - 0.09 mg/100 ml) but is uniquely well absorbed and utilized, for reasons that are unclear. The lower calcium and phosphate concentrations in breast milk and the presence of lactoferrin may be partly responsible. However, the total amount of iron absorbed by breast fed infants is less than that absorbed by those receiving an iron supplemented formula, and by 9 months, there is evidence of iron deficiency in some breast fed infants, unless additional sources of iron are present in the diet [7].

Although the absorption of iron from iron supplemented formulas is less efficient than breast milk, the use of such formulas is a reliable way of preventing iron deficiency [8].

Etiology

Dietary factors

The early introduction of unmodified cows' milk as the major milk source at around 6 months of age is the most common dietary characteristic of infants found to have IDA at 1 year [9].

Substances that diminish the absorption of ferrous and ferric iron include phytates, oxalates, phosphates, carbonates, and tannates [10].

Hemorrhage

Bleeding for any reason produces iron depletion. If sufficient blood loss occurs, iron deficiency anemia ensues. The bone marrow is stimulated to increase production of hemoglobin, thereby depleting iron in body stores. Once they are depleted, hemoglobin synthesis is impaired and microcytic hypochromic erythrocytes are produced.

Malabsorption of iron

Prolonged achlorhydria may produce iron deficiency because acidic conditions are required to release ferric iron from food.

Extensive surgical removal of the proximal small bowel or chronic diseases (e.g. untreated sprue or celiac syndrome) can diminish iron absorption.

Clinical picture

- Pallor, Koilonychia, Decreased effort capacity ,Tachycardia, Cardiomegaly, Heart failure.
- Loss of appetite, Angular stomatitis, Atrophic glossitis, Dysphagia, Pica.
- Decreased immunity due to lymphocyte and leukocyte dysfunction.
- Irritability-malaise, Papilledema, Pseudotumor cerebri, 6th nerve palsy, Restless leg syndrome, Breath holding spell, Sleep disturbance, Attention deficit, Learning difficulty, Behavioral disorder, Decrease in perception functions, Retardation in motor and mental developmental tests.

Laboratory findings

- Complete blood count:
  - Hb, Hct: low according to age and gender
  - RDW > 14
  - RBC: low
  - MCV: Low according to age and gender

    When specifying the lower limit of MCV: 70+age (for > 10 years)

    (if MCV is < 72, generally abnormal)
  - MCH < 27 pg
  - MCHC < 30%
  - Thrombocytosis
  - Rarely: Thrombocytopenia, leukopenia
- Peripheral smear:
  - Hypochromia, Microcytosis, Anisochromia, Anisocytosis, Pencil cells
  - Rarely: basophilic stippling, target cells, hypersegmented neutrophils
- Serum ferritin < 12 ng/mL.
- Serum iron: < 30 mcg/dL may change with age, gender and other factors.
- TIBC > 480 mcg/dL may change with age, gender and other factors.
- Transferrin saturation (Iron/TBC x 100) < 16%.
- Mentzer index (MCV/RBC) < 13.

Some new methods have been developed to be used in definite diagnosis like zinc protoporphyrin (ZnPP), free erythrocyte protoporphyrin, serum soluble transferrin receptor (sTfR) and reticulocyte hemoglobin content [11].

Prevention

The American Academy of Pediatrics and the World Health Organization recommend [12].

- Prevention of premature delivery,
- Delayed clamping of the cord especially in premature babies,
- Exclusive breastfeeding in the first 6 months,
- Enrichment of foods with iron,
- Giving iron-rich formulas when breast milk is insufficient,
- Avoiding cow's milk in the first year of life,
- Screening infants in the 9 - 12th months,
- Giving solid foods in addition to breast milk at separate meals.

Treatment

The main principles in treatment of iron deficiency anemia include making the diagnosis, investigating the condition which causes iron deficiency and elimination of this condition, replacement of deficiency, improvement of nutrition and education of patients and families.

Therefore, increasing consumption of meat and meat products is very important in prevention and treatment of iron deficiency. The other foods rich in iron include egg, well-done legumes, green vegetables and dry fruit.

Oral iron treatment is preferred primarily because it is economical and has few side effects. Iron preparations may be found as +2 ferrous or +3 ferric forms. The ferric form has to be transformed into the ferrous form to be absorbed. Therefore, the biologically significant form is +2 ferrous iron. The most commonly used oral +2 ferrous iron preparations include ferrous sulphate, ferrous gluconate, ferrous fumarate and ferrous succinate.

The most commonly used treatment dose is 3 - 6 mg/kg/day.

The rate of iron absorption also depends on the severity of anemia. It reaches the highest values in the first month of treatment. Signs observed in patients including restlessness, loss of appetite and fatigue rapidly disappear with initiation of treatment. An increase in the reticulocyte count is expected on the 7 - 19th days of treatment. If an increase of 1 g/dL or more is observed in Hb after ten days, the diagnosis is correct. In this case, treatment can be continued for at least 2 months to fill iron stores. The treatment period should not exceed 5 months. If there is an insufficient increase after one-month treatment, incompliance, continuing blood loss despite iron replacement, disruption in absorption of iron, high gastric pH (use of antacids or H2 receptor antagonists), wrong diagnosis or inefficient iron preparation should be considered.

Parenteral iron treatment can be administered when oral iron treatment cannot be tolerated, in cases where anemia should be corrected rapidly and in gastrointestinal absorption disorders including celiac disease or inflammatory bowel disease [13].

Anemia of chronic disease

Anemia of chronic disease is a form of anemia seen in chronic infection, chronic immune activation, and malignancy. Anemia of chronic disease is usually a mild or moderate condition.

These conditions produce elevation of Interleukin-6, which stimulates hepcidin production and release from the liver, which in turn reduces the iron carrier protein ferroportin so that access of iron to the circulation is reduced.

Also, inflammatory cytokines promote the production of white blood cells on the expense of red blood cells production in bone marrow. This effect may be an important cause for the decreased erythropoiesis seen in anemia of inflammation, even when erythropoietin levels are normal, and even aside from the effects of hepcidin.

In the short term, the overall effect of these changes is likely positive: it allows the body to keep more iron away from bacterial pathogens in the body, while producing more immune cells to fight off infection. Almost all bacteria depend on iron to live and multiply. However, if inflammation continues, the effect of locking up iron stores is to reduce the ability of the bone marrow to produce red blood cells.

Anemia of chronic disease as it is now considered to some degree separate from the anemia found in renal failure where there is low levels of erythropoietin, or the anemia caused by some drugs (like AZT, used to treat HIV infection) that have the side effect of inhibiting erythropoiesis. In other words, not all anemias seen in people with chronic disease should be diagnosed as anemia of chronic disease.

Diagnosis

A diagnosis of anemia of chronic disease is made based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation and a variety of specialized tests.

While no single test is reliable to distinguish iron deficiency anemia from the anemia of chronic inflammation, there are sometimes some suggestive data.

In anemia of chronic inflammation without iron deficiency, ferritin is normal or high, reflecting the fact that iron is sequestered within cells, and ferritin is being produced as an acute phase reactant. In iron deficiency anemia ferritin is low [14].

Total iron-binding capacity (TIBC) is high in iron deficiency, reflecting production of more transferrin to increase iron binding; TIBC is low or normal in anemia of chronic inflammation.

Treatment

The treatment of anemia of chronic disease is directed toward the underlying disease. If the treatment of the underlying disease is successful, anemia usually improves or resolves completely without direct treatment of its own. Because the anemia is generally mild, transfusions usually are not required.

Efforts to treat the anemia by correcting the iron imbalance in the body with therapies such as iron supplements or vitamins have generally proven ineffective. In fact, such efforts can have negative impact on overall health. For example, iron supplementation is controversial because certain diseases such as cancer use iron to grow and spread and certain infections use iron as nourishment.

Erythropoietin can be helpful, but this is costly and may be dangerous. Erythropoietin is advised either in conjunction with adequate iron replacement which in practice is intravenous, or when IV iron has proved ineffective [15].

Autoimmune hemolytic anemia [AIHA]

Autoimmune hemolytic anemia is a group of disorders characterized by a malfunction of the immune system that produces autoantibodies, which attack red blood cells as if they were substances foreign to the body. Autoimmune hemolytic anemia is a rare condition in children yet it's the main cause of acquired extra corpuscular hemolysis in children [16].

In general, AIHA in children has a good prognosis and is self-limiting. However, if it presents within the first two years of life or in the teenage years, the disease often follows a more chronic course, requiring long-term immunosuppression, with serious developmental consequences [17].

Pathophysiology

There are two main types of autoimmune hemolytic anemia:

- Warm antibody hemolytic anemia (IgG mediated): The autoantibodies attach to and destroy red blood cells at normal body temperature 37 degrees.
- Cold antibody hemolytic anemia (cold agglutinin disease) (IgM mediated): The autoantibodies become most active and attack red blood cells only at temperatures below normal body temperature optimally at 0 - 4ºC.

AIHA can be primary, where no evidence for a secondary causative disorder exists; or secondary in which hemolytic anemia is directly attributable to many causes like post-infectious (EBV, mycoplasma), drug induced (penicillin, quinidine, a-methyldopa), or caused by chronic autoimmune disorders or an underlying malignancy.

The majorities of cases are acute and carry a better prognosis with the possibility of spontaneous resolution within 6 months. The remaining cases are chronic and typically more difficult to treat. Chronic AIHA is found more commonly in the extreme age groups including kids less than 2 and teenagers.

Laboratory findings

- CBC:
    - Normocytic, normochromic anemia.
    - Reticulocytosis (or rare reticulocytopenia).
    - Spherocytes, schistocytes, poikilocytes, polychromasia.
    - Normal WBC and Platelets.
- +DAT (Direct Antigen Test/Coombs test) – patients RBCs are washed and combined with anti-globulin, agglutination signals a positive result.
- Gamma DAT: IgG attached to RBC.
- Non-gamma DAT: C3 is attached, seen in IgM type.

Treatment

70 - 80% of patients who have AIHA present with acute symptoms and mild anemia and are more likely to have spontaneous remissions of the disease with resolution in 6 months, thus intervention may be minimal or unnecessary in these groups.

Patients that present with more chronic onset are more likely to have a relapsing and remitting course and will likely require treatment; however some can have spontaneous remissions in months or years. These patients are more likely to be very young or teenagers and should have secondary causes of the AIHA thoroughly investigated.

Transfusion, steroids, IVIG and splenectomy are used in more severe forms which is out of scope of this article [18].

Mild thalassemia

The thalassemias are a group of disorders resulting from absent or reduced production of globin chains in hemoglobin tetramer. α- and β-thalassemia are caused by different types of mutations in α- and β-globin genes located at short arms of chromosomes 16 and 11, respectively.

There are four genes controlling the production of alpha chain and only two genes controlling production of beta chain.

Alpha thalassemia

People whose hemoglobin does not produce enough alpha protein have alpha thalassemia.

There are four types of alpha thalassemia that range from mild to severe.

Silent Carrier State: (Only one faulty gene out of the four genes controlling production of alpha chain). Also called alpha thalassemia minima: This condition generally causes no health problems because the lack of alpha protein is so small that the hemoglobin functions normally. It is called "silent carrier" because of how difficult it is to detect. Silent carrier state is "diagnosed" by deduction when an apparently normal individual has a child with hemoglobin H disease or alpha thalassemia trait.

Alpha Thalassemia Trait or Mild Alpha Thalassemia: (Two faulty genes) Also called alpha thalassemia minor. In this condition, the lack of alpha protein is somewhat greater. Patients with this condition have smaller red blood cells and a mild anemia, although many patients do not experience symptoms. However, physicians often mistake mild alpha thalassemia for iron deficiency anemia and prescribe iron supplements that have no effect on the anemia.

Hemoglobin H Disease: (Three faulty genes) And Hydrops Fetalis or Alpha Thalassemia Major (four faulty genes) both cause severe anemia and thus exceed the scope of this article.

Beta thalassemia

People whose hemoglobin does not produce enough beta protein have beta thalassemia. There are three types of beta thalassemia that also range from mild to severe.

Thalassemia Minor or Thalassemia Trait: Here, the lack of beta protein is not great enough to cause problems in the normal functioning of the hemoglobin. A person with this condition simply carries the genetic trait for thalassemia and will usually experience no health problems other than a possible mild anemia. As in mild alpha thalassemia, physicians often mistake the small red blood cells of the person with beta thalassemia minor as a sign of iron-deficiency anemia and incorrectly prescribe iron supplements.

Thalassemia intermedia and thalassemia major both can cause more severe forms of anemia and thus are out of this article scope.

Combined alpha and beta thalassemia

The severity of thalassemia is usually attributable to alpha and beta chains imbalance. As in beta thalassemia the main cause of hemolysis is the precipitation of uncoupled alpha chain due to defective production of beta chain, it's generally believed that if a combined alpha and beta thalassemia mutation exists there would be resultant decreased free uncombined alpha chain and less hemolysis. This co-inheritance may modify the CBC and HbA2 parameters in β-thalassemia patients.

Diagnosis

- As benign forms of thalassemia are usually mild and confused with iron deficiency anemia, definite diagnosis would require blood tests.
- Iron study should help differentiate between both.
- Reticulocytosis more in thalassemia and reticulocytopenia in iron deficiency.
- Hb electrophoresis can help identifying thalassemia.
- Genetic testing helps in thalassemia diagnosis.

Treatment

Usually mild forms of thalassemia needs no specific treatment, yet it's of paramount importance to make the diagnosis and differentiate this from iron deficiency anemia as the latter require iron supplementation which should be avoided in cases of thalassemia.

Conclusion

Anemia is the most common hematological disorder affecting wide range of population worldwide. It has a variable range of causes some of which are truly benign and don't affect life expectancy while others can be really serious with major effects on the patients and require serious interventions up to bone marrow transplantations. Knowing the benign causes would save the patients unnecessary or faulty interventions. Here we discussed some of the most common causes of benign anemias:

- Physiological anemia of the newborn
- Iron deficiency anemia
- Anemia of chronic disease
- Autoimmune hemolytic anemia
- Mild thalassemia

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