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Anemia is defined as a reduction in red blood cell mass or hemoglobin concentration in blood. It is statistically differentiated from normal states as a hemoglobin concentration or hematocrit 2 SD below the mean for the healthy population adjusted for age and sex. Anemias may be classified based on the morphologic function of red blood cells and their size on a peripheral blood smear. Subcategories are microcytic, normocytic, and macrocytic anemias, but these are not mutually exclusive. In infants and children, the most common form of anemia is microcytic. A detailed history and physical examination with appropriate laboratory test results can help detect the correct cause of anemia in most patients. The objective of this article is to aid physicians taking care of children in conducting a proper evaluation to identify the correct cause of microcytic anemia.

Keywords: microcytic anemia; normocytic anemia; macrocytic anemia; hemoglobin; red blood cells

Anemia is defined as a reduction in red blood cell (RBC) mass or hemoglobin concentration in blood. It is statistically differentiated from normal states as a hemoglobin concentration or hematocrit 2 SD below the mean for the healthy population adjusted for age and sex.[1] The initial approach to a child who has been diagnosed as having microcytic anemia is a detailed history and physical examination to establish a likely cause. Patients with mild cases usually present without any symptoms or with few nonspecific complaints. Similarly, individuals with α- and β-thalassemia trait and those with silent disease are usually asymptomatic. Patients with chronic but gradually worsening anemia may not manifest overt symptoms secondary to compensatory mechanisms, and hemoglobin concentrations 3 or 4 g/dL below normal are well tolerated. In these situations, clinical manifestations occur only when the hemoglobin concentration drops below a critical level as a result of acute changes such as bleeding or infections, causing imbalance between synthesis and requirement. Microcytic anemia is most frequently detected as a part of routine office screening or when blood is obtained as a part of the workup for another illness.

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Symptoms and Signs in Patients With Microcytic Anemia

Various systemic symptoms such as excessive sleepiness, tiredness, irritability or inappropriate behavior, shortness of breath, decrease in exercise tolerance, palpitations, syncope, and orthopnea are seen depending on the severity and the rate of development of anemia. The following are some of the historical factors that are important when evaluating a patient with microcytic anemia, some of which are summarized in Table 1.

Age

Nutritional iron deficiency usually is seen after 6 months of age. However, prematurity predisposes to early development of iron deficiency as a result of an imbalance between iron availability and that needed for growth. Placental iron transport is an important determinant of initial endowment of iron in fetal life and is maximal in the third trimester.[2] This leads to lower total body iron levels in preterm infants compared with term infants at birth. In addition, iron absorption and assimilation are minimal in the first 2 months of age. Therefore, preterm infants would need to absorb more iron during the subsequent 10 months to attain status equivalent to that of a term infant by 1 year of age. This is difficult by food intake only, especially since these infants have increased needs for catch-up growth too. Therefore, gestational age at birth should be considered.

Table 1. Causes of Microcytic Anemia in Infants and Children

Iron deficiency
Nutritional
Bleeding (gastrointestinal, urinary, menstrual, or pulmonary such as idiopathic hemosiderosis)
α or β-Thalassemias (major, minor, or trait)
Hemoglobinopathy (with or without thalassemia)
Lead poisoning
Chronic inflammatory conditions
Sideroblastic anemia
Atransferrinemia
Copper deficiency

Children who have β-thalassemia major with nonfunctional β-globin genes (Cooley anemia) clinically present during the second half of the first postnatal year. This is the time when the dominant hemoglobin switches from hemoglobin F (α2 and γ2) to hemoglobin A (α2 and β2).[3] Disorders such as sideroblastic anemias usually manifest later in life.

Race/Ethnicity

Some disorders are more common among certain racial/ethnic groups; therefore, it is important to know the patient's ancestry. α and β Thalassemia syndromes are prevalent among Mediterranean, Middle Eastern, Indian, and African American patients. These disorders are a result of quantitative changes in globin synthesis. The clinical presentation of children with these disorders varies from asymptomatic to severely affected depending on the amount of globin chain production.

Hemoglobin S and hemoglobin C disorders are more prevalent among African Americans and Hispanics, while hemoglobin E disorder is seen most often among Southeast Asians. These types of hemoglobinopathies, which are the result of abnormal globin chains, cause significant microcytosis when associated with thalassemia. However, it is important to remember that the absence of any of these ancestral lineages does not rule out any disorder.

Diet

Dietary history is essential because nutritional iron deficiency is the most common cause of microcytic anemia. During the first 6 months of life, breast milk provides more adequate iron intake to meet iron requirements compared with cow's milk or unfortified infant formulas.[4] The basis for this lies in the fact that iron in breast milk has higher bioavailability and better absorption than cow's milk.[2,5] Cow's milk is also a poor source of iron (0.3-0.7 mg/L). Prolonged breastfeeding confers partial protection against the development of iron deficiency anemia; after 6 months of life, breastfeeding must be supplemented with iron-fortified foods. Between 6 months and 2 years of age, excess milk intake (>24 ounces/d) is the leading cause of iron deficiency. Cow's milk causes a delay in gastric emptying time, causing interference with absorption of adequate amounts of iron from other food sources such as infant cereals.[4] In addition, cow's milk may cause mucosal bleeding due to lactoglobulin sensitivity.[4] Therefore, precise documentation is imperative of the volume of milk intake and other sources of iron, vitamin B12, and folic acid in the diet (such as the type of meats, vegetables beans, and grains). Children older than 12 months should be limited to less than 16 ounces/d of cow's milk. A history of pica or pagophagia (eating ice) suggests the presence of iron deficiency or lead poisoning.

Newborn Genetic Screen

Newborn genetic screen identifies infants with sickle cell disease, other non-sickle cell hemoglobinopathies, and thalassemias. Therefore, possible conditions causing microcytic anemia such as hemoglobins C and E and β- and α-thalassemias may be identified by review of the genetic screen.[6,7] During the neonatal period, hemoglobin F (α2 and γ2) is the dominant hemoglobin. In α-thalassemia, because the quantity of α chains produced is less than that of the γ chains produced, 4 γ chains come together to form hemoglobin Bart. Therefore, the presence of hemoglobin Bart in a newborn screen indicates α-thalassemia, and the amount of hemoglobin Bart is proportional to the severity of α-thalassemia. Fetuses with α4 gene deletion develop hydrops fetalis in utero (severe anemia leading to high output failure and anasarca), which is fatal at birth (incompatible with life as no α chains are present).[3]

Chronic Blood Loss

Menorrhagia in adolescent girls and gastrointestinal blood loss (overt or occult) from inflammatory bowel disease and exudative enteropathy are important

when evaluating a patient with microcytic anemia. These should be considered in the differential diagnosis and inquired about.

Exposure to Lead

Microcytosis associated with lead poisoning is due to iron deficiency caused by 2 mechanisms, interference with iron absorption and inhibition of enzymes required for heme synthesis. There is also contribution from nutritional iron deficiency as a result of pica. Information should be gathered regarding the source of lead such as the age of the dwelling (especially in inner-city areas with older buildings containing residual lead in paint and plaster), the location of a domicile near a major highway or factory, or the presence of ceramic pottery or lead toy figures.

Chronic Inflammation

Microcytic anemia occurs in chronic inflammatory conditions such as cancers, chronic infections, and autoimmune disorders (including inflammatory bowel disease, juvenile rheumatoid arthritis, and connective tissue diseases). Cytokines produced secondary to chronic inflammation in these conditions cause accumulation of iron in storage sites and inhibit RBC proliferation and differentiation, affecting iron hemostasis.[8] The cause is usually apparent in children having anemia associated with these conditions.

Physical Evaluation

The physical examination is unremarkable in most children except for pallor that can be appreciated in conjunctiva, gums, creases of the palms, and nail beds (especially valuable in darker-pigmented skins). Other findings that are seen in a few patients are tachycardia, glossitis, nail bed changes, and a flow murmur. The presence of splenomegaly is seen in hemoglobinopathies and major thalassemia syndromes along with bony deformities. Other physical findings that can be used as clues toward finding a cause of microcytic anemia are summarized in Table 2.

Table 2. Physical Findings as Clues to the Cause of Microcytic Anemia

Organ Affected and Sign	Diagnosis
Skin	
Pallor	S and C hemoglobinopathies
Ulcers on lower extremities	Thalassemias
Facies	
Frontal bossing, prominence of malar and maxillary bones	Thalassemia major, severe iron deficiency
Eyes	S and C hemoglobinopathies
Pallor of conjunctiva	
Tortuosity of conjunctival and retinal vessels	
Mouth	Iron deficiency
Pallor of gums	
Glossitis and angular stomatitis	
Heart	
Tachycardia at rest	Iron deficiency, S and C hemoglobinopathies
Flow murmur, signs of cardiac failure	Severe anemia
Abdomen	
Splenomegaly	Severe thalassemia and hemoglobinopathies
Guaiac-positive stools	Milk protein allergy, inflammatory bowel disease, enteropathy
Hands	Iron deficiency
Pallor in palm creases and nail beds	
Koilonychia (spoon nails)	

Laboratory Evaluation

Anemia is initially identified on routine screening based on the hemoglobin concentration and hematocrit. To classify it further as microcytic, macrocytic, or normocytic anemia, other useful and simple laboratory tests such as complete blood cell count, RBC indices, and peripheral blood smear should be ordered.

Microcytic anemia is characterized by low hemoglobin concentration and hematocrit (2 SD below the age-appropriate mean), low mean corpuscular volume (MCV), and low mean corpuscular hemoglobin concentration. Table 3 gives the age- and sex-specific hemoglobin concentration, hematocrit, and MCV values for anemia.

In the presence of microcytosis, a useful tool is the index score by Mentzer.[9] It is calculated as the ratio of MCV to RBC count in millions, with scores above 13 consistent with a diagnosis of iron deficiency anemia and 13 or below consistent with thalassemias. However, this should be confirmed by further testing.

Table 3. Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume (MCV) Values in Anemia

Age, y	Hemoglobin Concentration, g/dL	Hematocrit, %[a]	MCV, fL
Children			
1-<2	11.0	33	70
2-4	11.0	34	73
5-7	11.5	35	75
8-11	12.0	36	76
Boys			
12-14	12.5	37	77
15-17	13.0	38	78
18	14.0	40	80
Girls			
12-14	12.0	36	78
15-17	12.0	36	79
ϵ18	12.0	37	80

[a]Adapted from *Nathan and Oski's Hematology of Infancy and Childhood*.[1]

Electronic cell counters provide a RBC histogram with each analysis, from which the RBC volume distribution width (RDW) is derived.[1,10] The RDW is a statistical value calculated as the ratio of SD to MCV times 100. Therefore, it is a measure of variation in RBC size, and a wide distribution reflects anisocytosis. A normal histogram is usually symmetric and ranges from 11.5% to 14.5%. The RDW increases with iron deficiency and is low in thalassemia traits. However, the RDW value can be normal in the presence of markedly increased MCV and a wide RBC distribution curve. Therefore, it has high sensitivity but low specificity, making it useful only in conjunction with MCV in narrowing the differential diagnosis. In addition, this is applicable to mean corpuscular hemoglobin concentration, which is also a calculated statistical value. Screening recommendation of iron deficiency anemia in children are given in Table 4.

Table 4. Screening Recommendations for Iron Deficiency Anemia in Children[a]

Source	Recommendation
US Preventive Services Task Force11	Insufficient evidence in asymptomatic children aged 6-12 mo
Centers for Disease Control and Prevention12	High-risk infants and preschool children and nonpregnant women of childbearing age
American Academy of Pediatrics 13	All infants between the ages of 9-12 mo and then 6 mo later, once a year from ages 2-5 y for children at high risk
American Academy of Family Physicians11	High-risk infants aged 6-12 mo and infants whose principal dietary intake is unfortified cow's milk
Ages for Screening	**Risk Factors**
Ages 9 to 12 Months and 6 Months Later (at Ages 15-18 Months)	Preterm or low-birth-weight infants Infants on a diet of non iron-fortified infant formula for >2 mo Introduction to cow's milk before age 12 mo Breastfed infants with a diet inadequate in iron after age 6 mo Consumption of >24 ounces/d of cow's milk Special health care needs (eg, medications interfering with iron absorption, chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery) From low-income families Migrant or recently arrived refugee children
Ages 2 to 5 years	Low-iron diet Limited access to food because of poverty or neglect Special health care needs

[a]The US Preventive Services Task Force11 found no evidence addressing the harms of screening children for iron deficiency anemia. Potential harms include false-positive results, anxiety, and cost; small potential harms of treatment with oral iron include gastrointestinal symptoms and unintentional overdose.

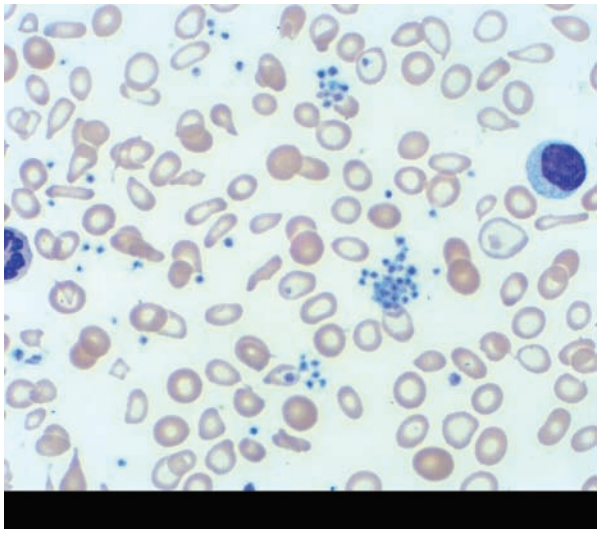

Figure 1. Hypochromic red blood cells with central pallor exceeding one-third of the diameter of the cell and hemoglobin restricted to the periphery.

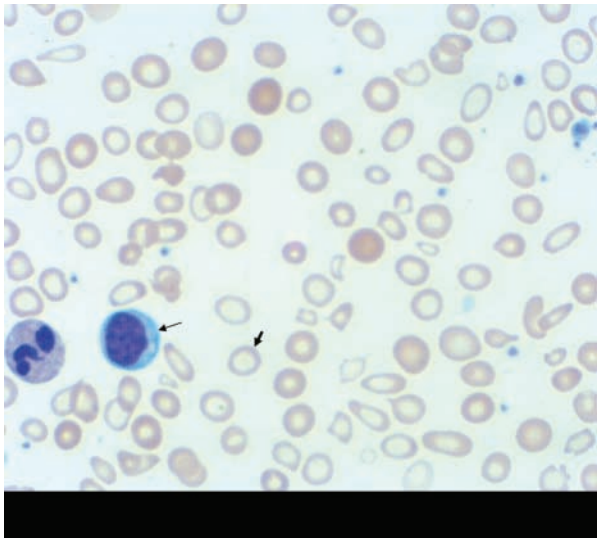

Figure 2. Microcytic red blood cells (thick arrow) compared with the size of a small lymphocyte nucleus (thin arrow).

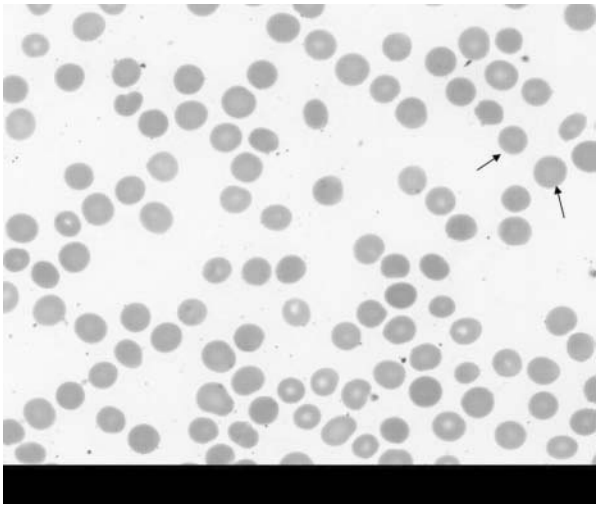

Figure 3. Spherocytes (arrows) as seen in hereditary spherocytosis characterized by spherical-appearing red blood cells that are smaller than normal red blood cells due to enhanced thickness and loss of the central clear zone.

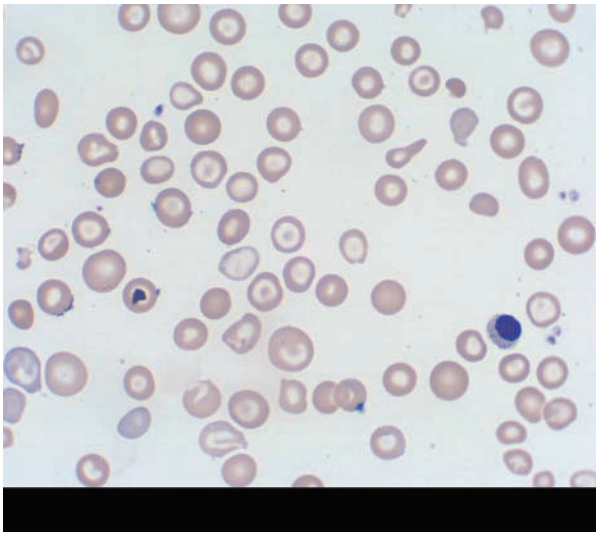

Figure 4. Target cell as seen in thalassemia syndromes with the periphery and central zone of the red blood cell rich in hemoglobin vs an intermediate rim devoid of color, giving it a target-like appearance.

Examination of a peripheral blood smear is the single most valuable procedure for initial classification of anemia and subsequently to narrow the diagnosis based on the erythrocyte morphologic structure. Cells are examined for their size, staining intensity, variation in color, abnormalities of shape, and presence of inclusions. The RBCs are hypochromic when their central pallor exceeds one-third of the diameter of the total cell (Figure 1). The size of normal RBCs approximately equals the size of a small lymphocyte nucleus; therefore, RBC size is usually compared with that size to determine microcytosis (Figure 2 and Figure 3). Pathologic findings found on peripheral smear such as various kinds of RBC inclusion bodies point toward the disease origin,

Table 5. Confirmatory Tests for Specific Causes of Microcytic Anemia[a]

Diagnosis and Laboratory Test	Result
Iron deficiency	
Serum ferritin, mcg/dL	Decreased
Serum iron, mcg/dL	Decreased
Total iron-binding capacity	Increased
Transferrin saturation, % (serum iron/total iron-binding capacity)	Decreased
Serum transferrin receptor, nmol/L	Increased
Free erythrocyte protoporphyrin, mcmol/mol	Increased
Bone marrow iron stores	Decreased
Stool for occult blood	Positive (gastrointestinal bleeding)
β-Thalassemia trait	
Hemoglobin electrophoresis	Increased A2 or F hemoglobin Decreased hemoglobin
β-Globin chain to α-globin chain ratio	<1
α-Thalassemia trait	
Hemoglobin electrophoresis	Normal hemoglobin electrophoresis
β-Globin chain to α-globin chain ratio	>1
Specific genetic probe analysis	Absent genes
Chronic inflammation	
Erythrocyte sedimentation rate, acute-phase reactants (C-reactive protein, fibrinogen, serum ferritin)	Increased
Serum iron and transferrin saturation	Decreased
Bone marrow iron stores	Increased
Lead poisoning	
Blood lead	Increased
Erythrocyte protoporphyrin	Increased

[a]Adapted from Segel.[14]

limiting further testing. The appearance of blue granules in the cytoplasm indicative of aggregated ribosomes is referred to as basophilic stippling and is seen in thalassemias, with unstable hemoglobins, and sometimes in lead poisoning. The presence of target cells is characteristic of thalassemias and hemoglobins S, C, and E (Figure 4). Other inclusions that can be present are Howell-Jolly bodies (nuclear remnants) seen in severe iron deficiency states and Heinz bodies (denatured or aggregated hemoglobin) present in thalassemia syndromes or unstable hemoglobins.

Reticulocytes are circulating immature RBCs, and an absolute count or percentage can help establish a cause of anemia. A low count indicates faulty bone marrow production, while a high count reflects a hemolytic process or active blood loss.

After the clinical evaluation and initial laboratory tests, a presumptive diagnosis can be made. More studies may be undertaken to yield a specific diagnosis if the findings are inconclusive or conflicting. Table 5 lists additional diagnostic tests needed to confirm the cause of microcytic anemia.

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