**Nutritional Anemias (2017 items)**

**Heeney**

1. Which of the following best characterizes the function of transferrin in iron metabolism?

A. A form of storage iron in intestinal mucosal cells

B. A form of storage iron in the tissues

C. A transport protein in the plasma

D. A receptor protein on the surface of erythroid progenitors

E. A key modulator of intestinal iron absorption

**Explanation**

One transferrin molecule binds and transports two atoms of ferric iron (Fe+++) from the intestinal mucosal cell or other sites to erythroid marrow, where it binds to membrane-bound transferrin receptors. Iron is stored in the tissues as ferritin or hemosiderin. The small amount of transferrin present in intestinal mucosal cells does not play a role in the storage of iron. Transferrin binds to an erythroid membrane receptor but is not itself the receptor. It also has no significant role in intestinal iron absorption. Answers A and B refer to ferritin. Answer D refers to transferrin receptor. Answer E refers to hepcidin/ferroportin.

2. A 7-month-old girl in excellent health has been exclusively breast fed. She has not yet begun to receive supplemental formula, cereal, or other solid foods. She takes no medications. Her physical examination is normal. Which combination of laboratory test results listed below would most likely characterize this patient?

A. Hemoglobin (Hgb) 9.0 g/dL, mean corpuscular volume (MCV) 58 fL, serum ferritin 7 ng/mL

B. Hgb 12.0 g/dL, MCV 80 fL, serum ferritin 30 ng/mL

C. Hgb 9.2 g/dL, MCV60 fL, serum ferritin 30 ng/mL

D. Hgb 11.2 g/dL, MCV 72 fL, serum ferritin 7 ng/mL

E. Hgb 9.8 g/dL, MCV 68 fL, serum ferritin 50 ng/mL

**Explanation**

Infants who are exclusively breastfed have depleted iron stores by 5 to 6 months of age. Iron deficient erythropoiesis begins soon thereafter, and frank anemia becomes apparent between 9 and 12 months of age. Therefore, a 7-month-old infant receiving no supplemental iron would be expected to exhibit a reduced serum ferritin (reflecting absent iron stores) but normal or only borderline low values for hemoglobin and MCV (as in choice D). Such an infant would not be expected to display a normal serum ferritin (higher than 10 ng/mL) or reduction in either hemoglobin or MCV (other choices).

All breastfed infants should receive iron supplements by 6 months of age. This can be iron-fortified cereal, iron-fortified formula, or ferrous sulfate drops. Although the iron in human breast milk is highly bioavailable (50% absorption), its concentration is so low (less than 1 mg/L) that the iron absorbed during the second 6 months of life does not meet demands resulting from rapid growth.

3. Assuming that adherence has been excellent, which of the following should have returned to normal 6 weeks following appropriate oral iron treatment of a child with severe dietary iron deficiency (hemoglobin 5.0 g/dL and mean corpuscular volume [MCV] 48 fL at the beginning of therapy)?

A. Hemoglobin concentration

B. MCV

C. Red cell distribution width (RDW)

D. Peripheral blood smear

**Explanation**

In uncomplicated nutritional iron deficiency, the hemoglobin concentration virtually always returns to the normal range within 6 weeks. The rate of hemoglobin rise often is quite dramatic. The MCV takes 3 months or so to return to normal. The RDW actually increases for the first 8 weeks following iron treatment as a result of a young population of large, well-hemoglobinized erythrocytes accompanying the older hypochromic microcytic cells from the iron-deficient state. The peripheral blood film, like the RDW and MCV, does not return to normal for 2 to 3 months.

4. As part of an oral iron absorption test, a child with unexplained anemia receives 2 mg/kg oral dose of elemental iron. Serum iron concentration before the iron dose is 20 μg/dL, and 1 hour later the serum iron concentration is 170 μg/dL. What is this child’s most likely diagnosis?

A. Hereditary hemochromatosis

B. Iron deficiency due to reduced dietary iron

C. Iron deficiency due to malabsorption

D. Anemia of inflammation

E. Upregulation of the transferrin receptor

**Explanation**

The baseline serum iron is greatly reduced, and a marked rise follows the oral iron dose. This indicates a diagnosis of iron deficiency and the expected increased absorption seen when it is due to either diminished iron intake or chronic bleeding. The serum iron would rise only minimally if malabsorption or inflammation were present. Patients with hereditary hemochromatosis and other forms of iron overload would have an elevated baseline serum iron concentration. Transferrin has no role in iron absorption.

5. Which combination of findings can result from a nutritional copper deficiency?

A. Microcytic anemia and neutropenia

B. Macrocytic anemia and lymphopenia

C. Normocytic anemia and thrombocytosis

D. Megaloblastic anemia with ring sideroblasts

E. Thrombocytopenia and eosinophilia

**Explanation**

Nutritional copper deficiency is extremely rare but, when present, results in microcytic anemia. This anemia is perhaps mediated by hephaestin, a transmembrane copper-dependent ferroxidase important in oxidizing Fe++ to Fe+++ and mediating iron efflux across the basolateral membrane of the duodenal enterocyte by ferroportin. The cause of the neutropenia accompanying copper deficiency is unknown. Copper deficiency also may produce vacuolated hematologic precursors in the bone marrow. The other combinations are not specific for any condition.

6. A 19-month-old infant with excessive whole cow milk intake has a hemoglobin of 8.7 g/dL and mean corpuscular volume (MCV) of 52 fL. Serum ferritin is 2 ng/mL. Hemoglobin electrophoresis shows HbA1 95%, HbA2 3.7%, and HbF 1.3%. What is the infant’s most likely diagnosis?

A. Iron deficiency alone

B. Iron deficiency plus alpha thalassemia trait

C. Iron deficiency plus beta thalassemia trait

D. Iron deficiency plus inflammation

E. Combined iron and folate deficiencies

**Explanation**

The HbA2 concentration is reduced in uncomplicated iron deficiency. In the setting of beta thalassemia trait *and* iron deficiency, the usually diagnostic elevated HbA2 can be “falsely normalized.” In this case, the child has clear biochemical evidence of iron deficiency (ferritin is 2 ng/mL), but the HbA2 remains borderline increased. This suggests that the child has beta thalassemia trait (where the HbA2 concentration in the absence of iron deficiency ranges from 3.5% to 7%) in addition to iron deficiency. Iron deficiency alone would have a normal HbA2. Alpha thalassemia trait would not elevate the HbA2. Chronic inflammation can result in iron deficiency but would not elevate the HbA2. Combined iron and folate deficiency might result in a normal MCV but with a wide red cell distribution width (RDW) and should have no effect on HbA2.

7. Which of the following laboratory test values is reduced in iron deficiency?

A. Serum transferrin

B. Free erythrocyte protoporphyrin (FEP) or Zinc protoporphyrin (ZPP)

C. Soluble transferrin receptor

D. Reticulocyte iron content (CHr)

E. Absorption of iron following an oral dose of iron

**Explanation**

Reticulocyte iron content may be the most sensitive early hematologic indicator of iron deficiency, usually noted before any changes in the blood count. Serum transferrin, FEP/ZPP, soluble transferrin receptor, and iron absorption all are increased in the setting of iron deficiency.

8. Iron-refractory iron deficiency anemia (IRIDA) is a rare inherited abnormality characterized by congenital iron deficiency anemia, a poor response to oral iron, and partial but incomplete response to intravenous iron therapy. IRIDA most commonly involves the inappropriate expression of which of the following?

A. Hemoglobin

B. Hemojuvelin

C. Hephaestin

D. Hepcidin

E. Hemosiderin

**Explanation**

In patients with IRIDA, mutations in TMPRSS6 disrupt the “iron sensor” and result in inappropriately high levels of hepcidin, even in iron deficiency. The constitutively elevated hepcidin results in iron-restricted erythropoiesis by impaired release of iron into the plasma from both duodenal enterocytes and RE macrophages. Hepcidin exerts its effect on these cells by binding and degrading ferroportin, the only known cellular iron exporter; therefore, there is no “pump” to bring iron into the plasma, where it is then bound to transferrin. Hemojuvelin is another protein involved in the iron sensor, but mutations cause inappropriately low hepcidin and juvenile hemochromatosis. Hephaestin is the transmembrane copper-dependent ferroxidases in the brush border of the duodenum that oxidized ferric (Fe+++) iron into the more readily absorbable ferrous (Fe++) form. Hemosiderin is a poorly bioavailable/pathological form of intracellular iron that is composed primarily of denatured ferritin.

9. Which of the following is a physiologic role of hepcidin in iron homeostasis?

A. It enhances iron absorption from intestinal mucosal cells.

B. It inhibits the production of interleukin-6 (IL-6) by macrophages and T-cells.

C. It enhances the oxidation of ferrous to ferric iron to facilitate iron binding to transferrin.

D. It inhibits iron release from macrophages.

E. It is a form of storage iron in hepatic parenchymal cells.

**Explanation**

Hepcidin is a small peptide made in the liver that appears to have an antiinflammatory function. Its production is induced by IL-6 but does not inhibit it. Its role in iron metabolism is to block iron transport from intestinal mucosal cells and macrophages by binding to and degrading ferroportin. It is a key mediator in the pathogenesis of anemia of inflammation (chronic disease). Answer D accordingly is the only correct answer that makes sense.

10. Which one of the following is the optimal method to monitor transfusion iron overload?

A. Bone marrow biopsy

B. Serum ferritin

C. Magnetic resonance imaging

D. Lung function

E. Liver biopsy

**Explanation**

MRI is the current optimal direct and noninvasive method to quantify the hepatic and cardiac iron burden. Bone marrow biopsy and liver biopsy are invasive, and bone marrow biopsy only provides a qualitative assessment of iron status. Although liver biopsy can be quantitative, it is subject to sampling error and may not be reflective of iron loading in other organs (eg, cardiac iron). Serum ferritin is a widely available and simple laboratory test, but any one elevated value can be reflective of acute phase reaction or tissue/hepatocellular injury. Iron overload has no significant direct effect on lung function.

11. A 14-year-old female student of Chinese descent with a history of 2° amenorrhea presents to an emergency room with rapidly evolving cardiac failure, a marked transaminitis, transferrin saturation (TfSat) of 98% (normal range, 20% to 50%), and a serum ferritin of 3,548 µg/L (normal range, 18 to 200 µg/L). CBC and RBC indices are normal.

What is the most likely genetic cause of iron overload?

A. Hemojuvelin (HJV)

B. HFE

C. Ferroportin 1 (FPN1) loss of function (“classical ferroportin disease”)

D. Non-transfusion dependent beta thalassemia (intermedia)

E. Alpha thalassemia trait

**Explanation**

The early age of iron loading and severe end-organ toxicity is most consistent with a juvenile form of hereditary hemochromatosis with mutations in HJV or hepcidin (HAMP) itself. HFE hemochromatosis rarely presents before the third decade of life. The normal CBC and RBC indices exclude thalassemia syndromes. Ferroportin disease related to loss of function generally results in milder iron loading with accumulation in the macrophages of the RE system, high ferritin, low TfSat and mild anemia.

12. A 14-year-old Greek girl recently has been diagnosed with systemic juvenile rheumatoid arthritis. Which of the following iron studies is most consistent with this clinical presentation?

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Hemoglobin (Hgb) | Mean Corpuscular Voume (MCV) | Transferrin Saturation (TfSat) | Serum Ferritin | Urinary Hepcidin |
| Normal Range | 12.0-16.0 g/dL | 78-102 fL | 20%-50% | 18-200 mcg/dL | 15-200 ng/mg Cr |

A. Hgb 11.8 g/dL, MCV 79 fL, TfSat 25%, serum ferritin 70 mcg/dL, urinary hepcidin 25 ng/mg Cr

B. Hgb 12.2 g/dL, MCV 82 fL, TfSat 25%, serum ferritin 70 mcg/dL, urinary hepcidin 25 ng/mg Cr

C. Hgb 11.8 g/dL, MCV 79 fL, TfSat 15%, serum ferritin 18 mcg/dL, urinary hepcidin 10 ng/mg Cr

D. Hgb 11.8 g/dL, MCV 82 fL, TfSat 15%, serum ferritin 328 mcg/dL, urinary hepcidin 220 ng/mg Cr

**Explanation**

All of the answer options present very similar RBC indices. Early iron deficiency can be difficult to distinguish from ß-thalassemia trait on the basis of RBC indices alone. Iron studies, hemoglobin electrophoresis, and clinical response to oral iron therapy can assist in making this distinction. The anemia of inflammation can be distinguished from iron deficiency and ß-thalassemia trait by the dissociation of the serum ferritin (high) from the transferrin saturation (low). Like ferritin, hepcidin also is an acute-phase reactant and is increased in inflammatory states. The increase in hepcidin and its effect on iron homeostasis is one of the contributing factors to the anemia of inflammation.

13. An 11-year-old girl is referred because of severe anemia. Three weeks ago she had two molars removed in preparation for braces. During the last week, she has had a marked increase in fatigue and shortness of breath associated with low-grade temperatures to a maximum of 101 °C.

The patient had neonatal hyperbilirubinemia requiring phototherapy, and since she was approximately 3 years old, her mother has noted pallor and intermittent jaundice. Her new pediatrician has one previous well-child bloodwork with hemoglobin (Hgb) 10.7 g/dL, reticulocytes 5%, with indirect bilirubin 3.5 mg/dL.

On exam, her temperature is 99.3 °C, respiratory rate is 27 bpm, and heart rate is 110 bpm. She has a red rash on her cheeks and a lacy red rash on her torso and extremities. There is a grade III/IV systolic ejection murmur along the left sternal border, not previously appreciated. Her spleen has been palpable 4 cm below the left costal margin and is not tender.

Her CBC now reveals Hgb 5.2 g/dL, reticulocyte count 0.7%. WBC and platelet count are normal. Her peripheral blood film reveals a high proportion of spherocytic red cells.

What is the most likely explanation for her recent drop in Hgb?

A. Coxsackie B virus infection

B. Parvovirus B19 infection

C. Systemic lupus erythematosus

D. Subacute bacterial endocarditis

E. Infectious mononucleosis

**Explanation**

The child has a reasonably well compensated chronic hemolytic anemia (likely HS based on the peripheral smear) with what appears to be an aplastic crisis. Although other intercurrent illnesses (eg, cocksackie and EBC/CMV) can result in increased hemolytic rate and/or decrease marrow production, parvovirus B19 is directly cytotoxic to colony-forming units (CFU-E) and burst-forming units (BFU-E) of the erythroid series. In individuals with an increased RBC turnover, even a limited cessation of RBC production related to parvovirus B19 infection can lead to a clinically significant drop in hemoglobin and transient aplastic crisis. Although the child has had dental procedures and a murmur, subacute bacterial endocarditis (SBE) does not fit the chronic hemolysis picture. Similarly, although a facial rash may evoke thought of systemic lupus erythematosus (SLE) and possibly a secondary autoimmune hemolytic anemia (AIHA) given the spherocytes, it does not explain the previous chronic hemolysis.

14. You are referred a 3-year-old boy with erythrocytosis. Upon further questioning, it appears there are other affected family members including one of three other siblings living in the same house and several other cousins in their native country. The boy has very low levels of plasma erythropoietin and no splenomegaly.

What is the most likely cause of this erythrocytosis?

A. Mutant hemoglobin having high oxygen affinity

B. Low levels of red cell 2,3-DPG due to an inactivating mutation of DPG mutase

C. Mutation of Epo receptor causing constitutive signaling

D. Carbon monoxide poisoning

E. Inactivating mutation of gene encoding von Hippel Lindau (vHL) protein

**Explanation**

High oxygen affinity hemoglobin (Hgb) variants result in elevated erythropoietin levels with normal PO2 and SaO2. Similarly low 2,3-DPG levels increase Hgb oxygen affinity and would result in elevated erythropoietin levels. Mutations in the hypoxia sensing pathway (eg, vHL gene mutations [Chuvash polycythemia], proline hydroxylase 2 [PHD2] loss-of-function mutations, and HIF-2 alpha [gain-of-function] mutation) also result in elevated erythropoietin.

Carbon monoxidepoisoning CO binds to the heme moiety thereby allosterically inhibiting oxygen release in tissues and shifting the oxyhemoglobin dissociation curve left. Also, although multiple family members are affected, some live outside the same house. Primary erythrocytosis includes inherited mutations leading to a constitutive RBC production independent of erythropoietin and includes rare autosomal dominant EpoRc mutations with constitutive positive signaling. The myeloproliferative neoplasm polycythemia vera is the most common acquired primary erythrocytosis; however, it very uncommon in children and especially if there is no associated splenomegaly.

15. A 6-year-old girl has exhibited increasing sluggishness with poorer school performance over the past year. She has no increased numbers of infections but now complains of headaches and abdominal pains. Physical exam shows no hepatosplenomegaly or lymphadenopathy. A CBC shows hemoglobin (Hgb) 10.8 g/dL, mean corpuscular volume (MCV) 71 fL, platelet count 293,000/mcL, and WBC count 8,160/mcL. Examination of her peripheral blood smear shows basophilic stippling of otherwise normal-looking erythrocytes. The serum haptoglobin is 25 mg/dL (normal, 30 to 200 mg/dL).

Which of the following laboratory test finding is most likely to be present in this girl?

A. HbS 94%, HbA 2 4%, HbF 2% on electrophoresis/high performance liquid chromatography (HPLC)

B. Increased osmotic fragility

C. Positive direct antiglobulin (Coombs) test

D. Decreased serum iron

E. Elevated free erythrocyte protoporphyrin

**Explanation**

This patient has lead poisoning. Lead directly inhibits delta-aminolevulinic acid dehydratase (ALAD), one of the enzymes necessary for heme biosynthesis, and therefore iron cannot be incorporated into heme. Lead also inhibits ferrochelatase, a mitochondrial enzyme causing erythrocyte zinc protoporphyrin and free erythrocyte protoporphyrin. The diminished heme synthesis leads to a hypochromic, microcytic anemia and a toxic injury resulting in aggregated ribosomes and mitochondrial fragments that appear as coarse basophilic stippling of red cells. Lead also can result in some low hemolysis and may be related to direct inhibition of pyrimidine 5′ nucleotidase.

Iron deficiency can lead to microcytic anemia but not with basophilic stippling. Autoimmune hemolytic anemia should result in complete consumption of haptoglobin and presence of spherocytes on the smear. The peripheral blood smear and relatively mild anemia is not typical of sickle cell disease.