HEMOGLOBINOPATHIES

Sickle Cell Anemia

Etiology and Overview[1,2]

- Autosomal recessive disease present at birth and most common inherited blood disorder in US, affecting approximately 100,000. Sickle cell disease (SCD) occurs among 1 in 365 African-American births and 1 in 16,300 Hispanic-American births, according to the Centers for Disease Control and Prevention,[3] with sickle cell trait found in about 1 in 12 African Americans and 1 in 100 Hispanic Americans.[2]
- More common among people with the following ancestry: sub-Saharan Africa; South America, Caribbean, and Central America; Saudi Arabia; India; and Mediterranean countries Turkey, Greece, and Italy.[3]
- Sickle cell hemoglobin, or HbS, due to mutation in hemoglobin-β gene (*HbS*) on chromosome 11 (valine is substituted for glutamic acid at position 6 of β globin chain, resulting in hemoglobin with solubility at low oxygen tensions); defective hemoglobin molecules (hemoglobin S) aggregate to form rod-like structures that block blood vessels, leading to multiple organ damage (spleen, kidneys, liver) and conditions including acute chest syndrome, pain episodes, priapism, stroke.
- Inheritance of 1 sickle globin gene leads to sickle trait (HbS); inheritance of 2 sickle globin genes leads to sickle cell anemia (HbSS).
  - HbS is most common variant worldwide, since malaria resistance is associated with heterozygous form.
  - HbSS is most common type of sickle cell disease.
  - Other variants/disease types: HbSC (second most common type, symptoms less severe than those of HbSS), sickle beta plus (Sβ+) thalassemia (mild form), sickle beta zero ($S\beta^0$) thalassemia (symptoms sometimes severe). Hemoglobin SD, SE, and SO are more rare types of sickle cell disease and not usually associated with severe symptoms. Different complications and indices, depending on type.
- Anemia caused by body's destruction of sickled cells.
- Sickling occurs at all times and can lead to organ damage.
- Increased infection risk in children, due to spleen damage.

Onset and Symptoms[1]

- Symptom onset typically occurs at 5 or 6 months; symptoms vary and change over time.
- Jaundice of skin and/or scleral icterus (with yellow hue due to elevated bilirubin levels).
- Fatigue, fussiness (due to anemia).
- Younger patients
  - Infancy/toddler: dactylitis (painful swelling of hands, feet)
  - Mostly < 5 years old: splenic sequestration crisis (splenomegaly, abdominal pain due to destroyed sickled cells trapped in spleen)
  - Aplastic crisis (can occur after viral infection and most commonly results from parvovirus B19–induced severe anemia [known as "fifth disease" in children])
  - Delayed growth and puberty
- Ongoing risks/complications
  - Severe and life-threatening anemia
  - Increased infection risk (particularly with chlamydia, HIB, salmonella, and staphylococcus)
  - Chronic pain and/or acute pain crisis (sharp or throbbing pain most commonly in abdomen, chest, lower back, arms/legs, due to vaso-occlusion by sickled RBCs)
  - Coronary heart disease and pulmonary hypertension
  - Chronic kidney disease
  - Acute chest syndrome (medical emergency caused by sickling in blood vessels of lungs and characterized by chest pain, fever, and dyspnea)
  - Joint and mobility problems due to avascular or aseptic necrosis (with pain especially in hips but also in shoulders, knees, ankles)
  - Gallstones
  - Detached retina (due to overgrowth, blockage, or bleeding of retinal blood vessels)
  - Silent brain injury/silent stroke (brain damage detectable on MRI but with no outward signs of stroke)

Diagnosis[1]

- Microscopic examination of blood sample to evaluate for large numbers of hemoglobin S. Technique can be used on amniotic fluid or placental tissue sample to determine if fetus has sickle cell disease or is carrier. Fetal testing for abnormal hemoglobin gene can be performed at 8–10 weeks. Pre-implantation genetic diagnosis (PGD) is technique for embryo testing for defective gene in conjunction with IVF, at discretion of parents who carry sickle cell trait. Newborn sickle cell disease screening analyzes blood obtained from heel prick. Done in all 50 states as part of routine screening.
- Blood screening tests to determine whether patient has sickle hemoglobin or another abnormal hemoglobin (SC, Sβ thalassemia, or SE).

Treatment and Patient Education[1]

- Bone marrow transplantation is only cure, but only about one-fifth of children with disease have healthy, matched sibling donor.
- Mainstays of treatment
  - Antibiotics, analgesic medications, blood transfusions (chronic for stroke prevention/severe illness or acute for anemia/surgery prep).
  - Regular vaccination, including annual influenza shot, essential and recommended regardless of whether patient is receiving treatment with penicillin. Pneumococcus PPSV23 (at 24 months of age and 5 years later) sometimes recommended in addition to PCV13. PPSV23 vaccine recommended if not received or at least 5 years have passed since vaccination with this vaccine.
  - Hydroxyurea: stimulates fetal hemoglobin, helping to prevent RBC sickling and reducing frequency of acute chest syndrome, need for blood transfusions.
  - L-glutamine (Endari; increases flexibility of RBCs, reducing risk of occlusion) approved July 2017 for treatment of SSD in patients 5 years old and older.
  - Pain control: Hydration and NSAID therapy (ibuprofen) or, for patients with renal dysfunction, acetaminophen, narcotics for severe pain. Many adults have chronic daily pain.
- Newer treatments
  - Voxelotor (oral hemoglobin S polymerization inhibitor, prevents Hb clumping) approved November 2019 for SSD patients 12 y/o and older; in phase 3 study, 51% of patients on 1500 mg dose had hemoglobin increase > 1 g/dL (regardless of hydroxyurea, baseline anemia; $P < .001$). Main AEs: headache, diarrhea. Avoid concurrent strong/moderate CYP3A inducers and CYP3A-sensitive substrates.
  - Crizanlizumab (IV anti-P-selectin MoAb), approved November 2019 for management of vaso-occlusive crises in SSD; benefit seen in patients with multiple SSD genotypes, 5–10 prior pain crises. Delayed time to first pain crisis even in patients already receiving hydroxyurea. May be of particular benefit in patients not wanting to undergo HSCT.

Prognosis/Outlook

- Prophylactic treatment and medical care have improved survival beyond 50 years in half of patients—remarkable given that until recent years patients did not survive childhood.[2] However, there is large variance in life expectancy depending on where you live. Disease worsens with age and QOL decreases.
- Trials of gene therapy under way, to replace defective gene with functional one via insertion into bone marrow; murine studies show promise.
- Advances in gene editing: Recent progress with CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia reported.[4]
- Promising research and treatment advances relevant to sickle cell disease (and beta thalassemia) include approaches to inhibit *BCL11A* gene (B-cell lymphoma 11A, potent silencer of fetal Hgb).[5,6]

References

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Beta-Thalassemia

Etiology and Overview[1-4]

- Also known as Cooley's anemia. Autosomal recessive disorder due to mutations in beta (*HBB*) globin genes; result is imbalanced production of beta hemoglobin chains, causing impaired erythropoiesis; wide genotypic (with > 200 associated mutations in *HBB*) and phenotypic variability in degree of chain imbalance determines severity.
- Can be inherited in autosomal dominant manner in small percentage of families; in such cases, signs and symptoms caused by only 1 mutated copy of *HBB* gene.
- Can occur in conjunction with another hemoglobinopathy.
- Prevalence estimated at 1 in 100,000 in general population; highest prevalence in people of Mediterranean, Middle Eastern, Asian descent.
- All 50 states screen for severe thalassemia as part of newborn screening.
- Severe cases require blood transfusions; increased risk of iron toxicity.
- Three classifications, based on clinical and laboratory findings
  - Beta-thalassemia minor is heterozygous/carrier state, typically asymptomatic with mild anemia.
  - Patients with compound heterozygosity or homozygosity classified as having beta-thalassemia intermedia if moderate anemia present (and may not need routine transfusions) and beta-thalassemia major if severe anemia and regular transfusions required.
- Main complications are iron overload and bone deformation (often in facial bones) due to extramedullary hematopoiesis if not regularly transfused; patients also at increased risk of abnormal blood clots, especially if history of splenectomy.

Onset and Symptoms[2]

- Beta-thalassemia minor generally revealed incidentally on routine CBC, with patients having no significant physical findings but mild symptoms of anemia.
- Beta-thalassemia major presents during transition from fetal (HbF) to adult (HbA) hemoglobin, between ages of 6 months and 2 years. Symptoms include irritability, feeding problems/failure to thrive, pallor, recurrent fever, diarrhea, and abdominal enlargement due to splenomegaly. In untreated/undertreated infants, symptoms/effects can be severe and include jaundice and hepatosplenomegaly, leg ulcers, poor musculature, and skeletal changes (frontal bossing, long-bone deformities).
- Beta-thalassemia intermedia onset and symptoms highly variable; can present in young children (eg, at 2 years, with delays in development, growth) or in adults (eg, with pallor, fatigue, pulmonary hypertension). Patient may be placed on chronic transfusion program to reduce symptoms and improve quality of life.
- Gallbladder disease (due to gallstones) is long-term complication of beta-thalassemia major and intermedia.

Diagnosis[2]

- Required: HEP (hemoglobin electrophoresis) or HPLC (high-performance liquid chromatography) showing abnormal percentage of HbA (generally decreased, with % dependent on individual genetics), HbA2 (generally increased by < 10%), variably increased HbF (but markedly increased in beta-thalassemia major, by 30%–95% or higher).
- Important to consider other possible causes of elevated HbA2: hyperthyroidism, deficiency of vitamin B12/folate, antiretroviral therapy.
- HEP, HPLC can also uncover other hemoglobinopathies in patients with beta-thalassemia trait. (HEP is normal in alpha thalassemia trait.)
- Globin gene analysis provides information regarding specific gene defects.
- CBC, peripheral blood smear findings nonspecific.
- Beta-thalassemia major CBC: microcytic hypochromic anemia (Hb < 7 g/dL), mean corpuscular volume (MCV) 50–70 fL, mean corpuscular Hb (MCH) 12–20 pg.
- Beta-thalassemia intermedia CBC: Hgb 7–10 g/dL, MCV 50–80 fL, MCH 16–24 pg.
- Beta-thalassemia minor CBC: elevated RBCs, reduced MCV and MCH, normal to mildly elevated RBC distribution width (RDW; in contrast to other microcytic hypochromic anemias like iron deficiency anemia and sideroblastic anemia, which have very high RDWs).
- Peripheral blood smear: shows microcytic hypochromic anemia, with teardrop and target cells, basophilic stippling; in severe forms, anisopoikilocytosis with numerous aberrant/nucleated RBCs.
- Major differential diagnoses: other hemoglobinopathies, iron deficiency anemia.

Treatment and Patient Education[2]

- Beta-thalassemia minor (carriers, generally asymptomatic; no treatment required): Consider genetic counseling, prenatal diagnosis as appropriate.
- Beta-thalassemia major: regular RBC transfusion, with goals of achieving posttransfusion Hgb levels of 13–14 g/dL (pretransfusion Hb of 9.5–10 g/dL. May need to be higher depending on patient symptoms and needs), suppressing erythroid expansion, alleviating anemia symptoms, inhibiting gastrointestinal absorption of iron.
- BMT, cord blood transplant are the only potentially curative options in patients with severe disease.
- Major treatment complications due to overstimulation of bone marrow, reduced erythropoiesis, transfusion-related iron overload requiring treatment with chelation therapy, heart failure, atrial fibrillation, endocrine effects, thromboembolic events. Less frequently, transfusion-related infections (hepatitis B and C, HIV).
- Optimal management requires multidisciplinary care team that includes hematologists, nurses specializing in beta-thalassemia.
- Luspatercept–aamt (Reblozyl; activin II receptor trap) approved November 2019 for adult patients with beta-thalassemia who require regular RBC transfusion; decreases transfusion requirement.[5]

Prognosis/Outlook

- Prognosis poor before 2000; outlook much improved due to improved understanding of pathophysiology of beta-thalassemia, plus newer noninvasive techniques to measure organ levels of iron early in disease course, development of improved iron chelators and blood safety measures.
- Drugs under investigation as potential treatments for beta-thalassemia include agents that stimulate production of fetal Hgb, including hydroxyurea, 5-azacytidine, decitabine, and butyrate derivatives.[4]
- Promising research and treatment advances include approaches to inhibit *BCL11A* gene (B-cell lymphoma 11A, potent silencer of fetal Hb); and therapies aimed at improving iron dysregulation (minihepcidin, TMPRSS6 inhibitors), especially in patients who are not transfusion-dependent.[6,7]

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