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Sickle Cell Disease

Special Considerations in Pediatrics

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Objectives

- **Review pathophysiology of sickle cell disease**
  - Hemoglobin structure and function
- Recognize patient with sickle cell disease
- Understand major complications of sickle cell disease and how to ameliorate or treat them

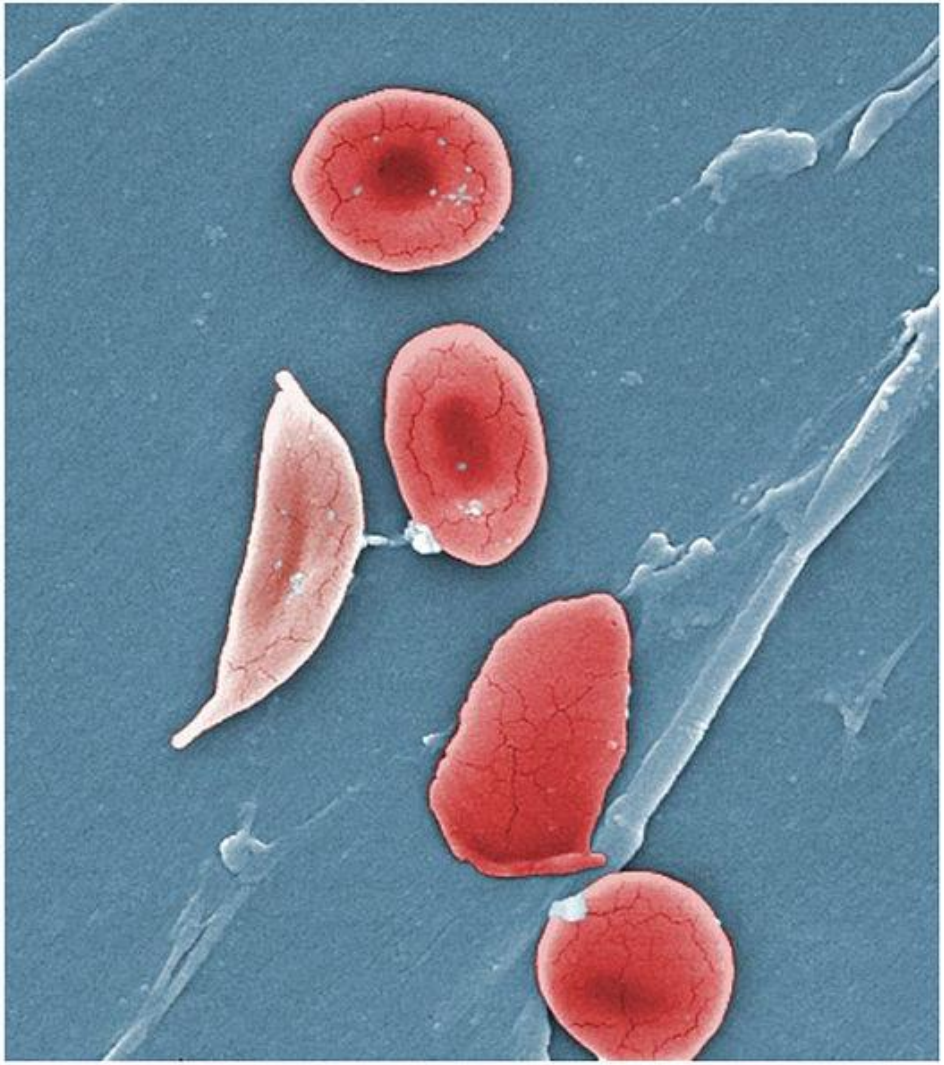
Disorders of Hemoglobin Structure and Production

- Sickle hemoglobin syndromes
  - Sickle cell anemia (SS)
  - Hemoglobin S-hemoglobin C (SC) disease
  - Hemoglobin S-β-thalassemia
- When hemoglobin S is <30% of the total hemoglobin sickling is unlikely

Hemoglobin Structure and Production

- In the fetus:
  - Hemoglobin F ($\alpha_2\gamma_2$)
- After birth:
  - Hemoglobin A ($\alpha_2\beta_2$) – The most common with a normal amount over 95%
  - Hemoglobin A_2($\alpha_2\delta_2$) – δ chain synthesis begins late in the third trimester and, in adults, it has a normal range of 1.5–3.5%
  - Hemoglobin F ($\alpha_2\gamma_2$) – Typically very small proportion, but Hb F can be elevated in persons with sickle-cell disease and beta-thalassemia

Sickle Hemoglobin



Resistance to Malaria

- Sickled hemoglobin (even in heterozygotes) gives resistance to *Plasmodium falciparum*
- Prevalence of sickle cell trait estimated to be up to 40% where malaria is endemic

Hemoglobin Structure

- Sickle cell hemoglobin differs from normal hemoglobin by a single amino acid
  - Valine replaces glutamate on the surface of the Beta chain
- In sickled cells hemoglobin tetramers stick to each other, forming long fibers (polymers) instead of remaining independent
- These polymers distort RBCs into abnormal sickle shape
- Heterozygotes have a mixture of normal Hgb A and abnormal Hgb S
  - Hemoglobin A stops polymerization, preventing serious sickling
- Red cell lysis occurs in homozygotes causing sickle cell 'anemia'

Hemoglobin Structure

- Anemia is not present at birth but develops by 4 months of age as hemoglobin F is replaced by hemoglobin S
- In the oxygenated state, hemoglobin S can function normally, but when it is deoxygenated, polymers more likely to form and lead to distorted cell shape
- Sickle cells are destroyed and cause increased blood viscosity, obstructing flow in small vessels leading to crisis

Objectives

- Review pathophysiology of sickle cell disease
  - Hemoglobin structure and function
- **Recognize patient with sickle cell disease**
- Understand major complications of sickle cell disease and how to ameliorate or treat them

Sickle Cell Diagnosis

- Consider in children with:
  - Unexplained pain or swelling (especially of hands or feet)
  - Pneumonia
  - Meningitis
  - Sepsis
  - Neurologic abnormalities
  - Splenomegaly
  - Anemia

Sickle Cell Diagnosis

- Hemoglobin level and reticulocyte count are inadequate screening tests
- Peripheral smear may lack sickled cells
- Hemoglobin electrophoresis definitive test
  - Takes several days to result

Objectives

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Major Complications

- Infections
  - Particularly susceptible to encapsulated organisms
    - *Haemophilus influenza* type b (Hib)
    - *Streptococcus pneumoniae* (pneumococcus)
    - *Neisseria meningitidis* (meningococcus)
    - Group B *streptococcus* (GBS)
    - *Klebsiella pneumonia*
    - *Salmonella typhi*
- Sickle cell crises
  - Vasoocclusive
  - Sequestration or Aplastic
  - Chronic organ damage

Major Complications

- **Infections (GOAL: antibiotic therapy)**
  - Sepsis, meningitis, osteomyelitis, septic arthritis
- **Sickle cell crises (GOAL: pain management, supportive care)**
  - Acute chest (treat as if associated infection – pneumonia)
  - Vasoocclusive crisis
  - Priapism
  - Stroke (may be silent)
  - Splenic sequestration
  - Aplastic crisis
  - Papillary necrosis
  - Hepatobiliary crises
  - Avascular necrosis

Sepsis

- Early loss of normal splenic activity
- Risk of bacterial sepsis increased several hundredfold in comparison with normal population
  - Pathogens in young children
    - *Streptococcus pneumonia* and *Haemophilus influenzae*
  - Pathogens in older children
    - *Escherichia coli* and *Salmonella*
  - Mortality from bacteremic episodes can be as high as 20-30%
- Period of greatest risk between 6 months and 5 years when development of protective antibodies is limited and splenic function is diminished or absent

Sepsis

- Children with hemoglobin SC or SS disease are prescribed prophylactic penicillin (or erythromycin if penicillin allergy) through age 5 years to prevent *S. pneumoniae* sepsis
- Help prevent serious infections with vaccines
  - Pneumococcal (*S. pneumoniae)*
  - Hib (*H. influenzae*)

Sepsis

- Fever
  - Must distinguish between SBI and benign, self-limiting viral disorders
  - All patients with sickle cell and fever should receive a basic laboratory evaluation
    - Malaria testing (when endemic)
    - CBC
    - Blood culture
    - Consider: urine analysis, culture, throat culture
    - Low threshold for obtaining a chest x-ray to screen for new infiltrates
  - Cornerstone of management in ED is rapid initiation of antibiotics after obtaining appropriate cultures

Sepsis

- Disposition
  - Routine admit, prolonged observation or outpatient
  - General rule out sepsis admission practiced
  - Close follow up at discharge, even after rule out
  - Ampicillin or third-generation cephalosporin given IV until culture results negative
  - Young children (<2yo) are at higher risk of bacterial sepsis and may be more difficult to assess for early signs of sepsis than older children
  - Temperatures >39-40°C suggest increased likelihood of sepsis

Sepsis

- Treatment of ill-appearing child with sickle cell disease, fever and probable sepsis, should include:
  - Antibiotic therapy
  - Management of septic shock
    - Fluid resuscitation
    - Pressors
- Clinical deterioration may be extremely rapid
- RBC transfusion or exchange transfusion may be needed to correct severe anemia or reduce secondary organ damage caused by massive sickling in presence of hypoxia, stasis and acidosis

Infections

- Level of suspicion for meningitis should be particularly high in the young, irritable child with sickle cell disease and unexplained fever
- Septic arthritis and osteomyelitis can be a diagnostic dilemma as mimics findings of infarction of the bones (vasoocclusive crisis)
  - The presence of other sites of concurrent infarction and patient's description of pain as typical "crisis pain" may be helpful in identifying cause as vasooclusive crisis
  - Predisposition to *Salmonella* osteomyelitis may be associated with areas of bone necrosis

Acute Chest Syndrome

- Includes pneumonia as well as pulmonary infarction
- One of most common reasons for hospital admission of children with sickle cell anemia
- Symptoms:
  - Oxygen saturation below patient's baseline
  - Symptoms of respiratory distress
  - New finding on chest radiograph
  - Fever is often present

Acute Chest Syndrome

- Management:
  - Antibiotic therapy
    - Third-generation cephalosporin
    - Macrolide
  - Consideration of RBC transfusion
    - Simple transfusion if hematocrit has fallen or is having evidence of severe or rapidly progressive disease
    - Exchange transfusion to decrease %HbS without raising hematocrit
  - *Treatment with steroids not usual part of regimen unless patient has a history of asthma and signs of asthma exacerbation
  - Pain control

Vasoocclusive Crisis

- Management:
  - Pain control
  - General supportive measures
  - Differentiation of vasoocclusion and disorders unrelated to the hematologic abnormality
- Keys:
  - Timely and efficient use of pain control early in the crisis has been shown to decrease the length of hospital stays
  - Initiation of PCA (patient controlled analgesia) in appropriate patients while still in the ED
  - Admission to the hospital warranted if continued pain despite parenteral analgesia
    - Prolonged stays in the ED rarely prevent hospital admissions

Vasoocclusive Crisis

- Dactylitis
  - Between 6 and 24 months of age
  - Recur frequently, caused by ischemic necrosis of small bones
  - Swelling may persist for 1-2 weeks, even after pain resolved
- Infarction of abdominal and retroperitoneal organs
  - Hepatic infarct
    - Acute onset of jaundice and abdominal pain similar to symptoms of hepatitis, cholecystitis and biliary obstruction
    - Pattern of recurrence important to indicate need for cholecystectomy
- Occlusion of mesenteric vessels
  - Mimics appendicitis/other cause of acute abdomen

Priapism

- Prolonged erection lasting >4h
- Penis is edematous and tender, urination may be difficult
- Treatment:
  - Fluid therapy and analgesia
  - Early aspiration of the corpora
- Relationship between duration of priapism and later potency in boys is unclear

Stroke

- Affects 7% of children with sickle cell disease
- Early detection of cerebral vascular disease using transcranial Doppler screening may reduce the frequency of stroke by allowing preemptive use of long-term transfusion therapy
- Routine screening for silent strokes

Stroke

- Presentation
  - TIA to seizures to hemiparesis, coma and death
  - Physical deficits supported by CT imaging
- Management of ischemic stroke
  - IMMEDIATE 1.5 or 2-volume exchange transfusion as soon as blood is ready
    - Reduces likelihood of further intravascular sickling and may prevent extension of cortical damage
  - Long term transfusion therapy designed to maintain HgbS to less than 30%
    - Risk of recurrence is reduced from 70% within 3 years to 10-15% with therapy

Stroke

- Risks of long term transfusion therapy
  - Allosensitization
  - Infection
  - Iron overload

Stroke

- Alternative approaches
  - Stem-cell transplantation
  - Maintenance therapy with hydroxyurea
    - Increases the level of HbF
    - Prevents secondary stroke

Stroke

- Cerebral aneurysms occur in increased frequency in patients with sickle cell disease
- Usually affects teens or adults
  - May be related to local vessel damage
- Aneurysm often escapes detection until after major and often fatal subarachnoid or intracerebral bleeding
- Careful evaluation of patients with sickle cell disease and headaches or other neurologic findings (vertigo, syncope, nystagmus, ptosis, meningismus or photophobia)

Stroke

- Management
  - If aneurysm is accessible and bleeding persists, surgical intervention follows radiologic confirmation

Splenic Sequestration

- Life-threatening complication of sickle cell disease
- Sudden enlargement of the spleen with resulting sequestration of a substantial portion of the blood volume
- Requires presence of vascularized splenic tissue, so usually occurs before 5 years of age in patients with hemoglobin SS disease, later in patients with milder sickling disorders such as hemoglobin SC or S-β^0-thalassemia

Splenic Sequestration

- Presentation:
  - Left upper quadrant pain
  - Patient becomes pale, lethargic, disoriented and appears ill
  - Exam shows evidence of cardiovascular collapse, hypotension and tachycardia are common; spleen is enlarged from prior exam and hard
  - Hematocrit and hemoglobin is lower than prior and reticulocyte is increased
  - Neutropenia or thrombocytopenia may be present

Splenic Sequestration

- Management:
  - Early recognition is key
  - Rapid infusion of large amounts of normal saline or albumin to restore intravascular volume
  - Transfusion with pRBCs (5 to 10mL/kg, beginning carefully with 2 to 3mL/kg) is often required in more severe cases
    - Increases intravascular volume
    - Improves impaired tissue oxygenation
  - Reversal of shock and rising hematocrit signal improvement of a sequestration crisis
    - Spleen gradually becomes less firm and smaller

Aplastic Crisis

- Increased baseline bone marrow production of RBCs (hence high retic count) partially compensates for the shortened RBC survival in sickle cell anemia
- When erythropoiesis slows or ceases, this precarious balance is disturbed and hemoglobin level may fall

Aplastic Crisis

- Parvovirus
  - Most commonly causes erythroid aplasia
- Signs:
  - Progressive pallor unaccompanied by jaundice or other signs of hemolysis
  - Severe anemia may result in dyspnea and alterations in consciousness
- Laboratory
  - Hemoglobin level is unusually low
  - Reticulocytes are decreased or absent

Papillary Necrosis

- Hematuria that is usually sudden and painless, often persistent
- Recent trauma, streptococcal infection or recurrent UTI suggest other cause of hematuria
- Hypertension suggests presence of nephritis rather than simple vasoocclusion
- Urine micro
  - Abundant RBCs but no RBC casts
  - Pyuria and proteinuria in excess of what might be attributed to blood in urine are not present

Papillary Necrosis

- Management:
  - Measure hematocrit
    - If hematuria persistent, can precipitate drop in hemoglobin
  - Admission to hospital typically required for IV hydration
  - RBC transfusions are sometimes needed when hematuria is severe
  - Transfusions or exchange transfusions can be useful in shortening the course of persistent hematuria

Hepatobiliary Crises

- Cholelithiasis is the most common hepatic and biliary tract complication in children with sickle cell disease
  - 12% in 2 to 5 year olds
  - 40% by age 15 to 18
- Presentation:
  - RUQ pain and tenderness , hyperbilirubinemia, and elevated liver enzyme levels
- Treatment:
  - Elective laproscopic cholecystectomy after preparations for surgery (transfusions) and once acute inflammation has subsided
- Acute cholecystectomy is associated with a significant risk of complications

Hepatobiliary Crises

- Acute intrahepatic sickling or viral hepatitis can result in similar clinical picture
  - Massive hyperbilirubinemia
  - Elevated enzyme levels
- Fulminant hepatic failure with hepatic encephalopathy and shock can also occur as a rare, often fatal syndrome
  - Exchange transfusions may give some improvement

Avascular Necrosis

- Sickle cell disease is the most common cause of avascular necrosis of the femoral head in children
  - Particularly Hgb SS and coexisting α-thalassemia
- Older children experience pain crises in long bones and the back resulting in aseptic necrosis of the bone
- More common if hematocrit is high and the clinical course is severe, with frequent painful crises
- Treatment:
  - Options limited – bed rest, core decompression
  - Total hip replacement may be necessary for femoral avascular necrosis

Questions?

Sources

- Manual of Tropical Pediatrics. M.D. Seear. 2000.
- Textbook of Pediatric Emergency Medicine. Fleisher and Ludwig. 2010.