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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$_2$($\alpha_2\delta_2$) – $\delta$ 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

[Image: Sickle Hemoglobin cell image from OpenStax College (Wikimedia Commons)]
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
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• 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

• 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
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 vasoocclusive 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 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