REVIEW

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Complications of sickle cell anemia in adults: Guidelines for effective management

ABSTRACT

Thanks to improved treatment, most patients with sickle cell disease now survive long into adulthood, but they still face a lifetime of complications and crises, including chronic hemolytic anemia, vascular occlusions, pain, and the side effects of therapy. This article consists of guidelines for diagnosing and treating problems encountered in adult patients with sickle cell disease.

KEY POINTS

Patients with sickle cell disease plus alpha thalassemia may have milder anemia, lower reticulocyte counts, lower mean corpuscular volume, and higher hemoglobin A_2 levels than patients with sickle cell disease alone.

Management of sickle cell disease includes folate replacement therapy and blood transfusion.

Simple transfusion should be used for specific indications only, and as sparingly as possible.

During acute painful crises, patients should receive opioid analgesics in sufficient quantities. Hydroxyurea may decrease the frequency of these episodes.

TODAY, NEARLY ALL sickle cell disease patients survive well into their adult years, and eventually come under the care of an internist or primary care physician.

The disease is common: approximately 10% of African Americans asymptomatically carry one gene for it, and 0.3% carry two genes and therefore have the full-blown disease.

In its effects, sickle cell anemia spares no organ of the body. Patients face a lifetime of crises and complications due to chronic hemolytic anemia, vascular occlusion (TABLE 1), and side effects of treatment. As in any chronic disease, the primary care physician, by working closely with the patient and family, can increase the quality and duration of the patient's life.

Our understanding of the natural history of sickle cell disease has advanced significantly in recent years. This update focuses on how to recognize sickle cell complications, differentiate them from painful crises, and manage them properly.

HEMATOLOGIC COMPLICATIONS

The anemia of sickle cell disease is typically chronic-hemolytic in nature. Hemolysis is due to premature destruction of sickled red blood cells primarily in the reticuloendothelial system.[1] A common sequela of chronic hemolysis in sickle cell anemia is cholelithiasis, often requiring cholecystectomy.

Hematologic profile varies in different forms of sickle cell disease

The hematologic picture varies somewhat in the different forms of sickle cell disease.

Sickle cell anemia: a terminology overview

THE HEMOGLOBIN MOLECULE contains four heme units and four globin chains. There are four different types of globin chains: alpha, beta, gamma, and delta. Of the four chains in a hemoglobin molecule, two are always alpha, and the other two are either beta (in hemoglobin A, the normal adult form), delta (in hemoglobin A_2, a minor form), or gamma (in hemoglobin F, the fetal form).

Sickle cell disease arises from a mutation in the beta globin chain, specifically, a substitution of valine for the normal glutamic acid at position six. Persons who are homozygous for this mutation (ie, who inherit the abnormal gene from both parents) are said to have the "SS" genotype and produce no normal hemoglobin A. Instead, they produce mostly hemoglobin S and small amounts of hemoglobin F and hemoglobin A_2.

Under hypoxic conditions, hemoglobin S becomes much less soluble and polymerizes into rigid aggregates, causing the erythrocyte to assume a sickle shape. After repeated cycles of sickling, erythrocytes become rigid and cannot flex enough to squeeze through small capillaries. Sickle cells collect in the microvasculature of an organ and form a plug. Eventually, the surrounding organ tissue is starved for oxygen, and local tissue necrosis results. Most of the signs and symptoms of sickle cell anemia are related to this microvascular blockage and tissue necrosis.

Yet "sickle cell disease" is a generic term. A number of factors determine the severity of the clinical disease. For example, persons who are heterozygous for the sickle cell gene (ie, who inherited the gene from only one parent) produce both hemoglobin A and hemoglobin S, and are said to have the sickle cell trait. Such persons usually have no symptoms.

Other hemoglobin disorders often coexist with sickle cell disease, as described below. Remarkably, the coexistence of these disorders tends to attenuate the severity of the sickle cell disease.

Thalassemia is a mutation that impairs the synthesis of hemoglobin, but not its structure. Different forms affect the alpha and beta globin chains. As with sickle cell disease, patients can be heterozygous or homozygous for thalassemia. The term "β^+" indicates that production of the normal beta chain is decreased, whereas "β^0" indicates that the normal beta chain is totally absent.

Hemoglobin C is a structural variant in which the normal glutamic acid at position 6 of the beta chain is replaced by lysine. Combined with the sickle cell gene, it is known as hemoglobin S/C disease. Similarly, the sickle mutation plus hemoglobin O Arab gives rise to hemoglobin S/O Arab.

One or more of the four genes that code for alpha globin may be deleted, affecting the hematologic and clinical picture of sickle cell syndromes.[2–4] For example, patients with sickle cell anemia and with two alpha gene deletions have a higher incidence of avascular necrosis than do patients with no alpha gene deletions.[2–4]

Of the forms of sickle cell disease, sickle cell anemia is the most common, followed by hemoglobin S/C disease, sickle-β^+ thalassemia, sickle-β^0 thalassemia, and other combinations. In severity, sickle cell anemia generally ranks number one, followed by sickle-β^0 thalassemia, hemoglobin S/C disease, and sickle-β^+ thalassemia. However, this scheme does not always apply at the individual level, and a patient with sickle cell anemia may have mild disease, whereas an occasional patient with sickle-β^+ thalassemia may have severe disease.

In sickle cell anemia, erythrocytes typically have a normal volume and hemoglobin concentration (ie, they are normocytic and normochromic). The mean corpuscular volume is approximately 90 μm^3/cell (normal range 86 to 98 μm^3/cell.[2,3]) The plasma hemoglobin concentration is low, between 7.0 and 8.0 g/dL (normal range 14 to 18 g/dL for men, 12 to 16 g/dL for women). Both the white blood cell count and the platelet count are increased, due to increased marrow activity secondary to chronic hemolysis and,

TABLE 1

Complications of sickle cell anemia primarily due to vascular occlusion

Musculoskeletal
- Acute painful episodes
- Chronic painful syndromes
  - Leg ulcers
  - Avascular necrosis

Central nervous system
- Acute cerebral infarction
- Acute cerebral hemorrhage
- Seizures

Retinopathy

Cardiopulmonary
- High-output heart failure
- Mitral valve prolapse with mitral regurgitation
- Acute chest syndrome

Abdominal
- Splenic sequestration
- Acute hepatic sequestration
- Hepatic crisis

Genitourinary
- Priapism
- Hematuria
- Nephrotic syndrome
- Focal glomerulosclerosis

Iron deficiency anemia may be especially common in young menstruating women

in the case of platelets, to "autosplenectomy," in which platelets are not stored in the spleen. The reticulocyte count is typically elevated.

In sickle cell anemia with homozygous alpha-thalassemia, patients have milder anemia, lower reticulocyte counts, low mean corpuscular volume, and high hemoglobin A_2 levels.[2,4,5]

In hemoglobin S/C disease, patients typically have microcytic and hyperchromic red blood cell indices.[6]

In sickle cell disease with β^0 thalassemia, patients typically have microcytosis, hypochromia, high hemoglobin A_2 levels, and variable hemoglobin F values.

In sickle cell disease with β^+ thalassemia, the anemia is mild, usually with microcytosis and a hemoglobin level greater than 10 g/dL.

Hematologic crises in sickle cell anemia

Patients with sickle cell disease may develop other types of anemia.

Hyperhemolysis, or hyperhemolytic crisis, is characterized by a decrease in hemoglobin levels and an increase in the reticulocyte count, indirect bilirubin, and lactate dehydrogenase. Hyperhemolysis may be caused by infection (eg, *Mycoplasma* pneumonia), coexistent G6PD deficiency with exposure to oxidant stress, and delayed hemolytic transfusion reaction, and it may occur during the evolution of the sickle cell painful crisis.

Aplastic crisis is characterized by a decrease in both hemoglobin and reticulocyte values and is most commonly caused by infection, both bacterial and viral, especially parvovirus B19.

Megaloblastic crisis is occasionally seen in patients who develop folate deficiency because of poor dietary habits and no folic acid supplementation.

Iron deficiency anemia may complicate sickle cell anemia, especially in young menstruating women. Iron deficiency anemia may have a salutary effect on the phenotypic expression of sickle cell anemia because of impaired hemoglobin S polymerization secondary to a decreased mean corpuscular hemoglobin concentration.

Management of hematologic complications

Management of the anemia of sickle cell disease includes folate replacement therapy and blood transfusion.

Folic acid therapy is necessary because this vitamin becomes depleted due to enhanced erythropoietic activity secondary to chronic hemolysis. This deficiency is especially frequent in patients with poor dietary habits. Most patients with sickle cell anemia should be taking 1 mg of folic acid daily.

Folic acid therapy may have the additional benefit of reducing the homocysteine level. Hyperhomocysteinemia secondary to folate or vitamin B_{12} deficiency has been linked to peripheral vascular, cerebrovascular, and coronary thrombotic events. Recent reports suggest that folic acid may lower the risk of coronary artery disease and cerebrovascular disease by lowering the plasma homocysteine concentration.[7,8]

These new developments reinforce the role of folic acid in sickle cell disease.[9] A recent study suggested that high homocysteine levels may be a risk factor for cerebrovascular accidents in sickle cell patients.[10] Conceivably, in such patients, folic acid may prevent the accumulation of homocysteine that may predispose to the thrombotic events that lead to painful episodes or crises. This issue needs further study.

Patients taking folic acid regularly need to have their serum vitamin B_{12} levels checked periodically to rule out masked B_{12} deficiency. Patients taking phenytoin to treat seizures should also take folic acid daily to prevent phenytoin-related megaloblastic anemia.

Blood transfusion in sickle cell disease serves two main purposes: to improve oxygen-carrying capacity and transport, and to dilute circulating sickled red cells, improving microvascular perfusion.

Simple transfusion is indicated in the presence of:

- Hemoglobin concentrations less than 5.0 g/dL and significant signs and symptoms of anemia, especially in association with aplastic crises
- Angina or high-output heart failure
- Acute hemorrhage
- Acute splenic or liver sequestration
- Acute chest syndrome of mild or moderate severity
- Preoperative preparation with general anesthesia.

Exchange transfusion is usually indicated in the presence of potentially catastrophic organ failure, such as severe acute chest syndrome or acute cerebral infarction, as discussed below.

Paradoxically, transfusions could in theory increase the risk of painful episodes by increasing the hematocrit and, hence, blood viscosity. In patients with sickle cell anemia, the frequency of painful episodes is greater in those with a relatively high hematocrit than in those with a low hematocrit,[11,12] as a relatively high hematocrit increases the blood viscosity, which in turn predisposes the patient to recurrent vascular occlusion and, thus, more frequent painful episodes.

Most patients tolerate the chronic anemia of sickle cell disease well. In a case series, Jehovah's Witnesses (who do not accept blood transfusions) with sickle cell anemia tolerated severe anemia with hemoglobin levels as low as 2.7 g/dL.[13] These facts should alert physicians to exercise caution in giving transfusions to patients with sickle cell disease.

Special considerations with blood transfusion. Transfused blood should be screened and confirmed negative for hemoglobin S. Donor red blood cells should match at least the Rh and Kell phenotypes of the patient. Leukocyte-reduced red blood cell preparations are recommended, especially in children, because they reduce febrile reactions, decrease alloimmunization to human leukocyte antigens, and reduce the chance of transmitting cytomegaloviruses. (Children who are potential candidates for bone marrow transplantation should also receive irradiated cellular blood products.)

TABLE 2

Drugs used to manage pain in sickle cell disease

- **Nonopioid analgesics**
  - Acetaminophen
  - Nonsteroidal anti-inflammatory drugs
    - Ibuprofen
    - Naproxen
    - Ketorolac
  - Acetylsalicylic acid (aspirin)
  - Nonacetylated salicylates
    - Diflunisal
    - Choline magnesium trisalicylate
- **Opioid analgesics**
  - Weak opioid agonists
    - Codeine
    - Oxycodone
    - Dihydrocodeine and hydrocodone
  - Strong opioid agonists
    - Morphine
    - Hydromorphone
    - Meperidine
    - Oxymorphone
    - Levorphanol
    - Fentanyl
    - Methadone
- **Adjuvants**
  - Antihistamines
  - Antidepressants
  - Benzodiazepines
  - Phenothiazines
  - Antiemetics
  - Laxatives

Transfused blood should be negative for hemoglobin S

TABLE 3

Guidelines for managing acute painful crises in adults with sickle cell disease

- Believe the patient
- Identify precipitating factors if possible and treat accordingly (eg, prescribe antibiotics for infection)
- Periodically conduct a thorough clinical assessment, documenting pain severity, location, pain relief, and mood
- Select the appropriate opioid analgesic and its dose based on previous history
- Give opioid analgesics parenterally on a regular basis or by patient-controlled analgesia (maintenance dose)
- Monitor vital signs with special attention to the respiratory rate
- Taper or increase the maintenance dose of opioid analgesic
- Give rescue doses—one quarter or one half of the maintenance dose—for breakthrough pain
- Decrease or skip maintenance dose if the respiratory rate is less than 10 per minute
- Give nonopioid analgesics and adjuvants in combination with opioid analgesics
- Taper opioid analgesics gradually once the pain severity score decreases and the patient's mood improves
- Consider discharge once pain relief is achieved without medication or if pain is adequately controlled with oral medication
- Design a discharge and outpatient follow-up plan
- Give a prescription for enough analgesics to treat resolving or relapsing crisis pain

ACUTE PAINFUL EPISODES

Acute recurrent painful episodes, due to vascular occlusion in various organs but especially the bones, are the hallmark of sickle cell disease and the reason for more than 90% of hospital admissions in adult patients with sickle cell disease.

Treatment of these episodes is empiric and, depending on the severity of the pain, often consists of parenteral opioid analgesics. TABLE 2 lists analgesics commonly used in sickle cell pain crises.[14]

Treatment of severe pain in the emergency department and hospital should be aggressive and should follow specific guidelines (TABLE 3) within a multidisciplinary framework. Evaluation and assessment, choosing the appropriate type of medication, dose, and route of administration, and proper discharge planning constitute the major approaches to rational therapy.[14]

Preventing painful episodes

Measures to prevent or reduce the frequency of painful episodes include treatment with hydroxyurea and repeated blood transfusions.

Hydroxyurea, an anticancer drug, promotes production of hemoglobin F, the fetal form. In a double-blind, placebo-controlled trial, hydroxyurea decreased the frequency of painful episodes in most of the patients who took it.[15,16] The incidence of acute chest syndrome and the amount of blood transfused were also significantly less in patients who took hydroxyurea than in the placebo group.

Hydroxyurea has a narrow therapeutic window in the treatment of sickle cell anemia, and its effective dose is usually subtoxic. Moreover, patients may not experience any beneficial effects before 4 months of therapy.[15,16] Therefore, I recommend that a hematologist administer this drug and monitor the patient, determining the most appropriate dose on an individual basis. The initial dose in adults is 10 mg/kg/day.

Whether hydroxyurea decreases the frequency of acute painful episodes in sickle cell syndromes other than sickle cell anemia (ie, hemoglobin S/C disease, sickle beta-thalassemia) is not known.

Repeated blood transfusions may reduce the frequency of painful episodes in sickle cell anemia, but their role is controversial. In anecdotal accounts, transfusions reduced the number of hospitalizations and bacterial infections.[17] In a controlled study, Koshy and colleagues[18] found that pregnant patients who received transfusions had fewer painful episodes, but the outcome of pregnancy was no different. On the other hand, repeated blood transfusions can have several side effects, as will be discussed below.

ACUTE CHEST SYNDROME

Acute chest syndrome is the most common cause of death and the second most common cause of hospitalization in patients with sickle cell disease. The signs and symptoms—chest pain, fever, dyspnea, hypoxia, pulmonary

infiltrates, and decreasing hemoglobin levels—may be very mild or so severe as to be life-threatening. The syndrome may be caused by rib or sternal infarction,[19,20] pneumonia, pulmonary infarcts secondary to in situ sickling, fat or bone marrow embolism, or pulmonary embolism.

Repeated attacks of acute chest syndrome with pulmonary infarction predict the onset of pulmonary hypertension, pulmonary failure with cor pulmonale, and terminal acute respiratory distress syndrome.[21]

Diagnostic workup

The diagnostic workup should include chest radiography, sputum and blood cultures, serial arterial blood gas and hemoglobin levels, and ventilation and perfusion (V/Q) scans. The evaluation should also include a search for fat-laden macrophages in sputum or bronchoalveolar fluid obtained by bronchoscopy, and an evaluation to rule out thrombophlebitis in the pelvis or lower extremities.

Because acute chest syndrome is relatively frequent in sickle cell anemia, and in view of the need to monitor arterial blood gases in its management, one should establish the baseline levels of blood gases and pulmonary function tests in all patients, for future reference in evaluating patients who present with acute onset of pulmonary signs and symptoms.

Treatment

Treatment includes antibiotic therapy, oxygen, and, in severe cases, total blood exchange. Caution should always be exercised in giving opioids to hypoxic patients. Heparin is usually reserved for patients with proven pulmonary embolism.

CHRONIC PAIN SYNDROMES

Leg ulcers

Leg ulcers, which are painful and sometimes disabling, occur in 5% to 10% of adults with sickle cell anemia. They are more common in men and older patients, and less common in patients with alpha-gene deletion, high total hemoglobin levels, or high levels of fetal hemoglobin.[22]

Severe pain may necessitate the use of opioid analgesics. Wound care is with wet-to-dry dressings soaked in saline or Burrow's solution. With good localized treatment, many ulcers heal within a few months. Patients with leg ulcers that persist beyond 6 months may require blood transfusion or skin grafting, although results of skin grafting have been disappointing.

Leg ulcers may recur after minimal trauma. Special protective leggings, worn during working hours, appear to be an effective preventive measure.[23]

Leg ulcers occur in 5% to 10% of adults with sickle cell anemia

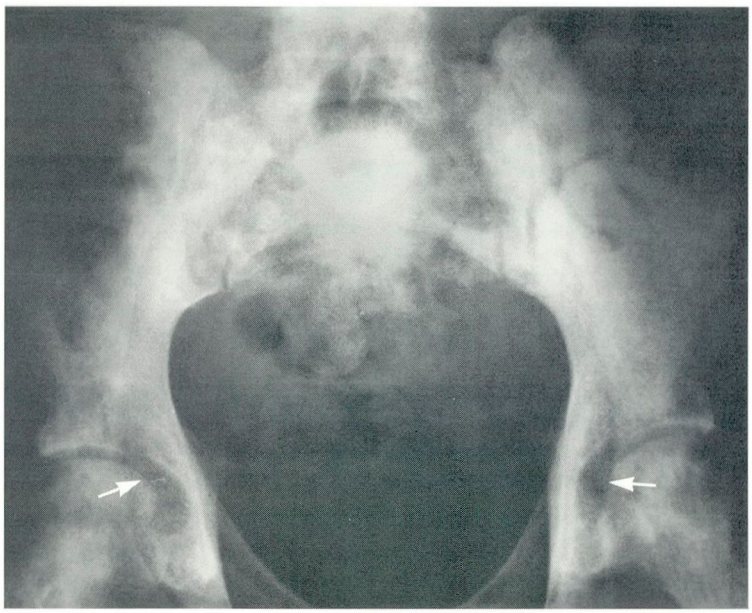

FIGURE 1. The pelvis and hips of a patient with sickle cell anemia show diffuse osteosclerosis of osseous structures, compatible with infarction. Avascular necrosis of both hips, without collapse of the femoral heads, is also evident (arrows).

Avascular necrosis

Avascular necrosis, also called ischemic necrosis or osteonecrosis, is the most common complication of sickle cell disease in adults.[24] Patients with sickle cell anemia and alpha-gene deletion have a higher incidence of avascular necrosis than do patients with sickle cell anemia alone,[3,5] because they tend to have a higher hematocrit, which increases blood viscosity and makes it more likely to clog the microscopic blood vessels in the bone.

Although avascular necrosis tends to be most severe and disabling in the hip (FIGURE 1), it may equally affect the shoulders and vertebral bodies as well. All three areas are espe-

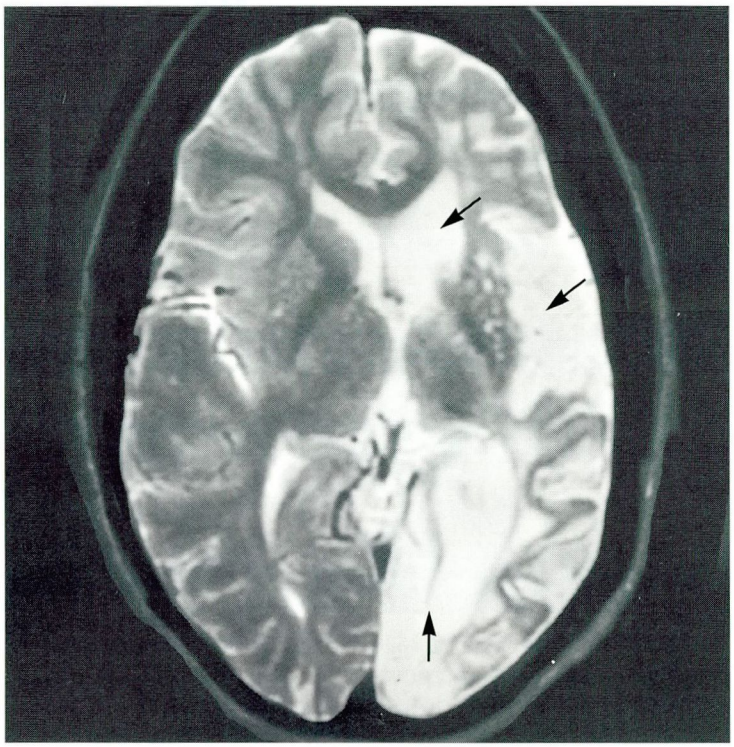

FIGURE 2. Magnetic resonance imaging of the brain of a patient with sickle cell anemia shows extensive encephalomalacia with secondary enlargement of the left lateral ventricle due to old infarcts in the distribution of the left middle and left posterior cerebral arteries (arrows).

cially vulnerable to sickling and subsequent bone damage because they have a limited terminal arterial blood supply and a paucity of collateral circulation.

Treatment of avascular necrosis is based on symptoms and includes physical therapy and nonopioid or opioid analgesics in the early stages. Advanced necrosis requires total bone replacement. Core decompression appears to be effective if done early.[25]

CENTRAL NERVOUS SYSTEM PROBLEMS

Neurologic complications occur in 25% of patients with sickle cell disease and are more common in sickle cell anemia than in other sickle cell syndromes, such as hemoglobin S/C disease and hemoglobin S beta-thalassemia.

Cerebrovascular events

Acute cerebral infarction is more frequent in children, whereas intracerebral hemorrhage is more prevalent in adults. Microaneurysms involving fragile dilated vessels, which develop as compensatory collateral circulation around areas of infarction, seem to be responsible for hemorrhage in adults.[24,26,27] Unlike in other vascular beds, large vessels rather than microvessels seem to be the site of occlusion with consequent infarction (FIGURE 2). About two thirds of children with cerebral infarction who do not receive blood transfusions may develop further ischemic events within 3 years.[27]

Transcranial ultrasonography of the large cerebral vessels may predict which patients are at risk for stroke. Prophylactic transfusion decreases the risk of a first stroke in children with sickle cell anemia with an abnormality on transcranial Doppler ultrasonography.[28]

Exchange transfusion or hypertransfusion is the appropriate therapy for children with cerebral infarction secondary to vascular occlusion, with a goal of maintaining hemoglobin S levels below 30%, and red cell transfusions are usually given for at least 5 years and possibly longer on an individual basis. It is not known, however, whether long-term transfusion therapy is indicated for adults with cerebral infarction secondary to vascular occlusion. Similarly, the appropriate management of an adult patient with cerebral hemorrhage is not known. A thorough search for aneurysms and consideration of surgical intervention is recommended.

Seizures

Seizures in sickle cell disease may be secondary to an epileptic focus from an infarction or treatment with large doses of meperidine over a prolonged time, or they may be idiopathic. Antiepileptic therapy is recommended for patients with electroencephalographic abnormalities.

RETINOPATHY

Sickle cell retinopathy results from occlusive arteriolar lesions in the retina that lead to microaneurysms and collateral neovascular proliferation ("sea fans")(FIGURE 3). This vascular damage is followed by vitreous hemorrhage and retinal detachment.

Sickle cell retinopathy is more common in hemoglobin S/C disease than in other sickle cell syndromes. Furthermore, the frequency of retinopathy is time-dependent and age-specific, and older patients are at higher risk.

Regular follow-up by an ophthalmologist is highly recommended, since photocoagulation therapy for early retinopathy may prevent progression to neovascularization, retinal detachment, and blindness.

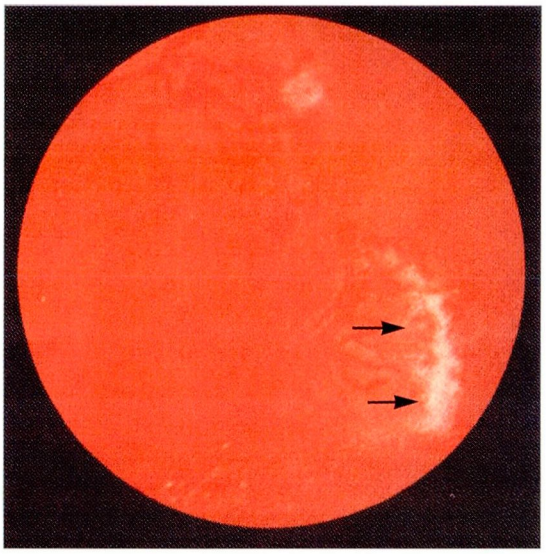

FIGURE 3. Fundoscopy of a patient with sickle cell disease shows the "sea fan" pattern of proliferative sickle cell retinopathy (arrows).

CARDIAC COMPLICATIONS

Cardiac manifestations in patients with sickle cell anemia include high-output heart failure, right heart failure, congestive heart failure, cardiac hemosiderosis, and cardiomegaly. Myocardial ischemia may also occur, and myocardial infarction has been reported.[29]

Although mitral valve prolapse was reported[30] to have a high prevalence (25%) in sickle cell disease, this finding was not confirmed by another study.[31] The signs and symptoms of mitral valve prolapse (chest pain, dyspnea, fatigue, syncope, palpitations) overlap with those of sickle cell disease and may imitate the protean manifestations of sickle cell disease. Patients with mitral valve prolapse and significant mitral regurgitation should receive prophylactic antibiotic therapy before dental procedures.

HEPATOBILIARY SYSTEM

At least two thirds of patients with sickle cell anemia have hepatomegaly, and 75% have cholelithiasis. About 90% of patients with cholelithiasis undergo cholecystectomy either prophylactically or after an episode of acute calculous cholecystitis.

Acute hepatic sequestration of sickled erythrocytes is characterized by hepatic enlargement associated with a significant fall in hemoglobin levels, but with no appreciable disturbance in liver function tests.[32]

Hepatic crisis, or "sickle cell intrahepatic cholestasis," is manifested by the sudden onset of right upper quadrant pain, progressive hepatomegaly, increasing bilirubin levels (mostly indirect), and prolongation of the prothrombin and partial thromboplastin times.[33] Levels of the liver enzymes gamma-glutamyl transpeptidase and alanine aminotransferase are also elevated, but not to the extent seen in acute viral hepatitis. Hepatic crises, like acute splenic sequestration, vary in severity from minor episodes to severe life-threatening situations. Total blood exchange, in which whole blood is removed and replaced with red cells and fresh frozen plasma, is recommended if the total bilirubin level increases progressively to values greater than 50 mg/dL. At that level, the prothrombin times are usually prolonged. Blood exchange should be continued until the level of hemoglobin S is reduced to less than 30% and the coagulation abnormality is corrected.

Two thirds of sickle cell anemia patients have hepatomegaly; 75% have cholelithiasis

GENITOURINARY SYSTEM

Urinary tract infections are usually caused by *Escherichia coli* and are more common in females than in males. Their increased frequency in sickle cell disease may relate to renal infarction or to immunodeficiency.

The hypoxic, acidotic, and hypertonic microenvironment of the renal medulla causes sickling of the red cells in the vasa recta and leads to infarction of the renal medulla, hyposthenuria, and hematuria (gross or microscopic). Inability to acidify the urine after an acid load can also occur. These renal tubular

defects (hematuria, hyposthenuria) occur not only in patients homozygous for the sickle gene, but also in heterozygous patients.

Hematuria

Management of hematuria in patients with sickle cell disease is conservative. Strict bed rest alone results in spontaneous remission in most patients. In a few instances, gross hematuria may be severe enough to warrant blood transfusion. Use of epsilon-aminocaproic acid and desmopressin acetate may effectively control hematuria.[34,35]

Impaired potassium excretion

Potassium excretion is also impaired, and episodes of hyperchloremic acidosis have been reported. Hyperkalemia may be spurious due to in vitro hemolysis of collected blood samples kept in the lab at room temperature for some time before analysis. Occasionally, hyperkalemia is reported in association with type 4 renal tubular acidosis (ie, acidosis due to hypoaldosteronism), but renal insufficiency is present in most of these patients.[35]

Priapism

Hematuria in sickle cell disease usually remits with strict bed rest

Priapism occurs when sickle cells congest the corpora and prevent the emptying of blood from the penis. It can result from tricorporal involvement (the corpus spongiosum and both of the corpora cavernosa) or bicorporal involvement (both corpora cavernosa only). The latter is more common in children and is not regularly associated with impotence.

Priapism has two major clinical presentations: acute and chronic. The acute presentation is a prolonged painful erection that persists beyond several hours, responds poorly to exchange transfusion, and frequently requires surgical intervention. Acute priapism may be followed by complete or partial impotence.

Chronic priapism consists of repetitive, reversible, painful erections called "stuttering" priapism. It usually occurs after intercourse or it may awaken patients early in the morning. Stuttering priapism responds well to diazepam or pseudoephedrine hydrochloride. Patients who become impotent may benefit from psychological counseling and the insertion of penile implants.

Nephrotic syndrome

Nephrotic syndrome, with or without hypertension, occurs frequently in patients with sickle cell disease. Microscopic hematuria, proteinuria, hypertension, and the nephrotic syndrome are markers of incipient end-stage renal failure. Proteinuria occurs in 26% of patients with sickle cell disease, and elevated serum creatinine occurs in about 7%.[36] The pathologic lesion is usually glomerular enlargement and peripheral focal segmental glomerulosclerosis.

Treatment with the angiotensin-converting enzyme inhibitor enalapril seems to reduce the degree of proteinuria in sickle cell disease, suggesting that capillary hypertension may be a pathogenic factor in sickle cell nephropathy. Once chronic renal failure progresses to end-stage renal disease, patients require chronic hemodialysis and are candidates for kidney transplantation.

Other complications

Papillary necrosis may be more common in hemoglobin S/C disease. Hyperuricemia in sickle cell anemia is the result of both increased bone marrow activity with consequent enhanced urate production due to purine metabolism, and an acquired decreased renal tubular clearance of urate. Gout has been described in a few patients. Allopurinol may be indicated to lower serum urate levels.

COMPLICATIONS DUE TO IMMUNOSUPPRESSION

Several acquired abnormalities render patients with sickle cell disease immunocompromised, and hence susceptible to a number of infections that are major causes of mortality and morbidity.

Need for vaccinations

Without a functioning spleen, patients are more susceptible to infection with polysaccharide-encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Thus, all patients with sickle cell disease should receive the polyvalent antipneumococcal vaccine every 3 to 5 years. (*H influenzae* type V conjugate vaccine is given only to infants, at ages 2, 4, and 6 months.)

Other recommended vaccinations, besides routine childhood vaccines, include influenza vaccine annually and hepatitis B vaccine at birth or at the first visit of children and adults who have no serologic evidence of previous exposure to hepatitis B virus.

Other problems

Cellular immunity may be compromised by transfusion-related iron overload, and abnormalities in B-cell immunity may explain antigen processing defects. Infections due to *E coli* are usually associated with urinary tract infections in women. Patients with sickle cell anemia are susceptible to osteomyelitis secondary to *Salmonella typhimurium*, in addition to the usual causes of bacterial osteomyelitis such as *Staphylococcus aureus*. The susceptibility to infection by *Salmonella* may reflect the ability of this organism to flourish in partially necrotic bone.

Individuals with sickle cell trait are resistant to infection by *Plasmodium falciparum*, but patients with sickle cell anemia are susceptible. In addition, individuals whose blood group profile includes Fy(a–b–) are resistant to infection by other types of malarial parasites.

COMPLICATIONS OF THERAPY

Some complications seen in patients with sickle cell disease are due to therapeutic interventions (TABLE 4).

Potential complications of blood transfusions are many. Of note:

- Patients who received transfusions before 1992, when a reliable second-generation screening test for hepatitis C was introduced in blood banks, may have acquired the hepatitis C virus.
- The transfusion of leukocyte-reduced components decreases the chances of alloimmunization. Transfusion of phenotypically identical red blood cells also minimizes the chances of HLA alloimmunization and hemolytic reactions.
- Iron overload is best monitored by periodic determination of serum ferritin in patients who receive frequent transfusions. Serum ferritin levels higher than 1,500 ng/mL are an indication for chelation therapy with deferoxamine.

TABLE 4

Potential complications of therapy of sickle cell disease

Complications of blood transfusions
- Allergic and febrile reactions
- Alloimmunization
- Hemolytic reactions
- Immunosuppression
- Iron overload
- Transmission of infectious disease

Complications of hydroxyurea
- Idiosyncratic reactions
- Myelosuppression
- Teratogenicity
- Unknown long-term effects (eg, possibly leukemia)

Complications of opioid therapy
- Addiction
- Constipation
- Dependency
- Emesis
- Euphoria
- Myoclonus, seizures
- Orthostatic hypotension
- Pruritus
- Respiratory depression
- Sedation
- Skin rash

Complications related to route of opioid administration
- Intramuscular
  - Infection
  - Fibrosis
  - Sterile abscess
- Implantable catheters
  - Infection
  - Septicemia
- Transdermal patches
  - Pruritus
  - Skin rash

In sickle cell patients, opioid addiction is unusual

Hydroxyurea-related myelosuppression is a major toxic effect of hydroxyurea therapy. Periodic monitoring of hematological parameters during therapy allows early detection and management of myelosuppression, which is reversible after discontinuation of hydroxyurea. Long-term effects of therapy with hydroxyurea are not known, but there is concern that it may promote leukemia.

Opioid therapy can induce respiratory depression, its most serious complication.

Addiction is the exception rather than the rule in patients with sickle cell pain treated with opioids. Furthermore, fewer than 3% of patients may manifest maladaptive behavior due to opioid therapy. Drug dependence should not be mistaken for addiction. It is a physiologic phenomenon characterized by signs and symptoms of withdrawal when opioids are discontinued.

Administration of opioids via totally implantable catheters is associated with a higher incidence of infection in patients with sickle cell disease than in other diseases.[37]

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