Consult a Sickle Cell Expert: How to Apply NIH Guidelines in Caring for Adult Sickle Cell Patients

Alecia Nero, M.D., M.S.C.S., F.A.C.P.
Assistant Professor
Department of Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
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This is to acknowledge that Alecia Nero, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Nero will not be discussing off-label uses in her presentations.

Alecia Nero, M.D., M.S.C.S., F.A.C.P.
Assistant Professor
Departments of Internal Medicine and Pediatrics
Division of Hematology-Oncology

Interests:

Dr. Alecia Nero is a dual-trained, internist and pediatrician who then completed hematology fellowship. She holds her primary appointment in the Department of Internal Medicine and secondary appointment in the Department of Pediatrics as an Assistant Professor. She works in the Division of Hematology-Oncology with clinical and research interests in non-malignant hematology, specifically focusing on sickle cell disease in children and adults. Dr. Nero is the Medical Director of the UT Southwestern Sickle Cell Day Treatment Program. She also leads the Sickle Cell Transition Program between the medical center's Pediatric and Adult clinics.

Purpose and Overview:

Sickle Cell Disease (SCD) is one of the most common inherited hematologic disorders. Most of the clinical advancements in the U.S. have occurred in childhood leading to high rates of survival to adulthood. The adult patient, however, remain at risk for many complications that can lead to significant morbidity and early mortality. Evidence-based research is sorely lacking in SCD. Further, there is lack of providers that are knowledgeable in caring for adults with SCD. This is likely multifactorial and include issues such as lack of interest in non-malignant hematology training. Specifically, there is a huge gap in trained providers with interest in caring for adults with SCD. Sickle cell experts and stakeholders made the conscious effort to try to provide support to non-experts who encounter these patients. In an attempt to fulfill this need a report on evidence-based guidelines in the care of these patients has been developed by the National Heart, Lung, and Blood Institute of the NIH. What is clearly observed in this report is the lack of such evidence-based research that still poses a dilemma in delivery of clinical care. Therefore, consensus statements were provided to allow some guidance for the target audience of the non-hematologist. An additional challenge in the recommendations is to identify sickle cell expertise to address the more complicated challenges that are most readily seen in the hospitalized patient. The purpose of this presentation is to first make internists aware of these guidelines. We will continue this discussion on how to approach some of the common challenges that are encountered when caring for the adult patient with SCD. By the conclusion of this presentation, the audience should be able to access available resources when caring for adult SCD patients and have a more broad understanding of the clinical complexities facing affected patients.

Educational Objectives:

1. To better understand Sickle Cell Disease as a disorder with significant medical complications other than pain
2. To provide internists resources in the management of adults patients with Sickle Cell Disease
3. To effectively utilize current guidelines in caring for adult patients with Sickle Cell Disease
4. To work toward breaking the stigma that impedes care delivery to adult patients with Sickle Cell Disease

Introduction and Clinical Features of Sickle Cell Disease

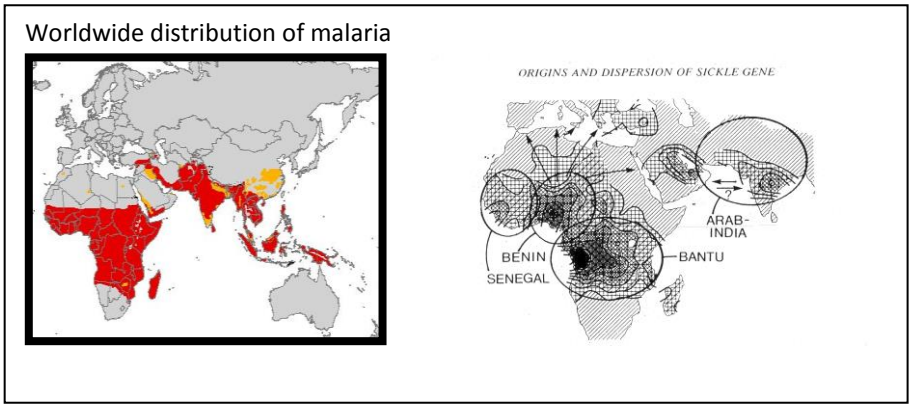
Alecia C. Nero, M.D., M.S.C.S., F.A.C.P.

History/Epidemiology

Sickle cell disease (SCD) is a group of disorders with the commonality being the inheritance of abnormal hemoglobin, one of which is the "sickle" hemoglobin (Hb S). There have been early descriptions of SCD in West Africa for generations with first reports documented in the 1800s. The credit for detailed clinical and microscopic evaluation of this disease has been given to Dr. James Herrick after his intern's, Dr. Ernest Irons, assessment of a dental student revealed abnormally shaped red blood cells which were described as "sickle-shaped". This article was published in a medical journal in 1910, therefore establishing the first published detail of sickle cell disease in North America [1]. It was not until some years later after additional reports of similar cases that Dr. Morton coined the term "sickle cell anaemia" [2].

A carrier of the sickle hemoglobin mutation affords protection against malaria infection. It is proposed that natural selection allowed this gene to persist in malaria-laden regions of the world, therefore resulting in the geographic distribution of SCD (Figure 1).

Figure 1. Malaria influence on global distribution of sickle gene

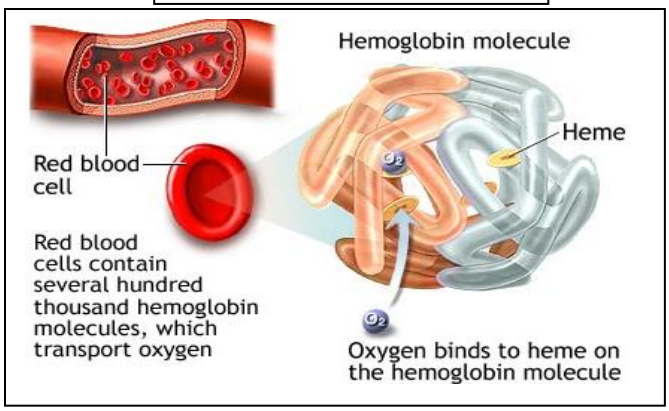


The current global estimate of the prevalence of SCD ranges in the millions. Although SCD is not exclusively a disease of ethnic minorities, this environmental influence results in a predominance of affected Mediterranean, Middle Eastern, Indian, Latin American, African and Arabian individuals.

Pathophysiology

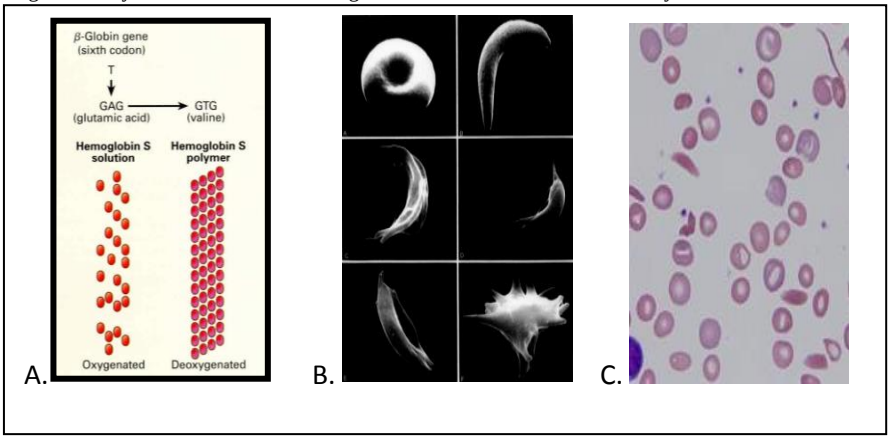
Hemoglobin is a macromolecule (MW-64,000) consisting of two pairs of unlike polypeptide chains (α and non-α), each with an iron-containing heme moiety that is packaged within red

Figure 2. Hemoglobin and red blood cell



blood cells (rbcs) (Figure 2). Its primary role is in gas exchange between the tissues of the body and the lungs and produced by bone marrow erythroid progenitors. These globin chains switch during different points in pre- and post-natal development until the final adult hemoglobin is achieved. The beta globin locus resides on chromosome 11 and inherited in an autosomal recessive fashion. The point mutation causing the sickle hemoglobin occurs at the sixth position on the beta globin gene. The consequence of this mutation is replacement of the normal glutamic acid residue with a valine residue that causes the pathology noted in the sickle cell syndromes. The sickle cell syndromes include the homozygous (hemoglobin SS) or an array of compound heterozygous states which also may have regional bias. Given the change from a hydrophilic amino acid to the hydrophobic amino acid that gets transcribed, rigid polymers can form that lead to characteristic shape changes of the rbcs. These rbcs are not in a stagnant state but can cycle between their sickle and non-sickle shapes (reversibly sickled cells) until they become irreversibly sickled (Figure 3). These cells become unstable and have shortened lifespan which leads to the hemolytic anemia characteristic of SCD.

Figure 3. Polymerization of S containing cells between sickle and irreversibly sickle state

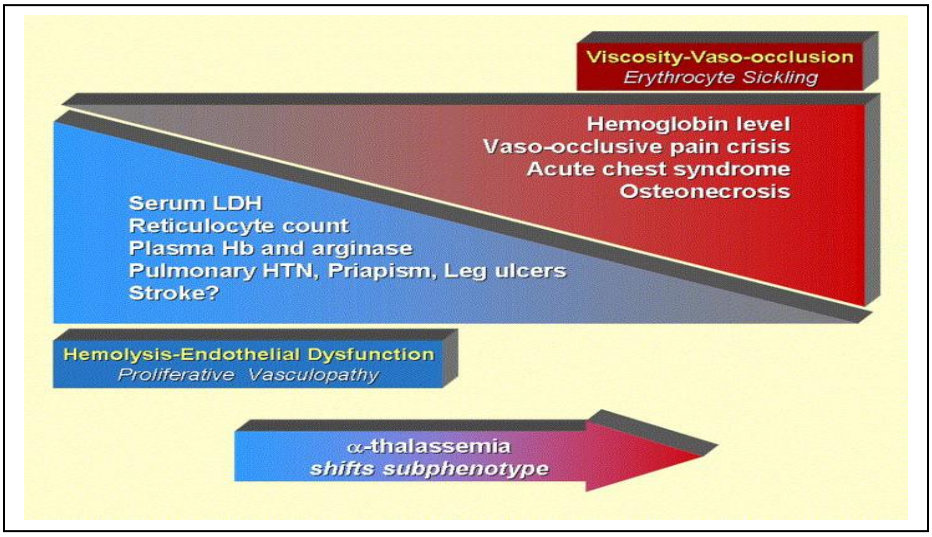


Although SCD is on one level a disease of rbcs, this clearly does not explain the range of complications of disease. It is widely known that the various clinical manifestations as well as laboratory findings are consistent with a disease process that is very active in the inflammatory,

coagulation and endothelial pathways [3]. Further, these interactions include vasculopathic as well as cytokine/chemokine interactions that can lead to damage of every organ system in affected individuals. Current drug trials are targeting such pathways to treat complications of sickle cell disease based off the noted preclinical and early human studies [4].

Given these interactions, there have been proposed subphenotypes of SCD (Figure 4). Specifically, the viscosity-vaso-occlusion subphenotype vs. the hemolysis-endothelial dysfunction subphenotype has been described[5]. The proposed mechanism of action with the viscosity-vaso-occlusion model is based on the micro-vascular obstruction in capillary beds directly caused by the rigid rbcs. The result of this interaction leads to ischemia-reperfusion injury, tissue infarction, and disturbance in appropriate cell adhesion which culminates in an inflammatory response. The clinical complications caused by these effects are what results in pain events, elevated white blood cell counts, acute chest syndrome and avascular necrosis. The hemolysis-endothelial dysfunction pathway is proposed to be the mechanism by which patients suffer from strokes, priapism and leg ulcers due to the downstream effects of free heme scavenging available nitric oxide.

Figure 4. Sickle cell disease subphenotypes[5]



Classification and Diagnosis

The sickle cell genotypes are described by the denoting the hemoglobin gene that is inherited with the sickle hemoglobin. As mentioned earlier, homozygous disease or hemoglobin SS is the most common variant. However, there are several other genotypes and some are listed in Table 1.

Table 1. Classification of Sickle Cell Syndromes

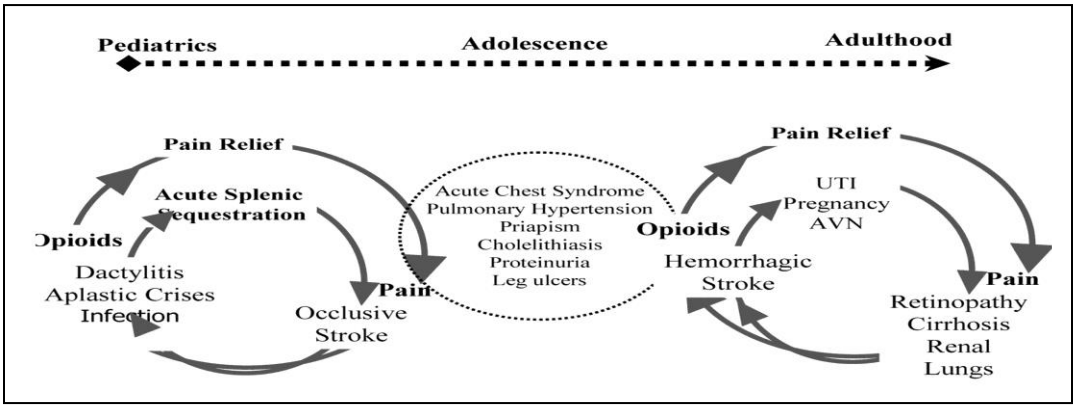
Inherited Genes	Notation
Homozygous S	Hb SS
Sickle- hemoglobin C	Hb SC
Sickle- β^0thalassemia	Hb Sβ^0thalassemia
Sickle- β^+thalassemia	Hb Sβ^+thalassemia
Sickle- hemoglobin D Punjab	Hb SD Punjab
Sickle- hemoglobin O Arab	Hb SO Arab
Sickle- hemoglobin E	Hb SE

All U.S. states perform universal screening of newborns that includes testing for early diagnosis of SCD as early intervention is imperative in their care. Hemoglobin electrophoresis historically was the preferred diagnostic test, but more commonly high performance liquid chromatography and isoelectric focusing techniques are used. Formal DNA testing is also being used on a much larger scale. Sickle cell trait (SCT), or the carrier status (Hb AS), is mentioned only briefly as it is not sickle cell disease but has been part of controversial recommendations mandating testing of college athletes. SCT does not lead to the clinical disease manifestations but in rare circumstances has been implicated in spleen infarcts, aggressive renal medullary carcinoma and renal complications. Recommendations to test for establishing carrier status should be primarily based on the importance of allowing patients to be aware when making reproductive choices.

Clinical Complications

The range of clinical complications of SCD is quite variable and, as mentioned earlier, can affect every organ system (Figure 5). Some of these tend to be more common in childhood vs. adulthood or vice versa. Some also tend to present in certain genotypes more than others but this too is a generalization. For example, it is widely accepted that the Hb SS and Hb Sβ^0 genotypes tend to have more clinically severe phenotype. Any complication can occur at any point in a patient's lifespan and should remain on the differential diagnosis as this tends to be an unpredictable disease.

Figure 5. Spectrum of Clinical Complications in Sickle Cell Disease



INFECTION

Patients with SCD are at increased risk for serious bacterial infections which was previously the leading cause of death. However, due to improved clinical practice and preventive care, this is no longer the primary cause of death in this country. Daily prophylactic penicillin is recommended within the first months of life and continued for at least the first five years in children with the severe genotypes. All children and adults are recommended to be up to date on specified vaccines. Infection does remain a significant cause of death in developing countries where such practices have not yet been fully employed. The spleen is one of the earliest organs that sustain damage in the young child with SCD. This functional asplenia is one reason for the susceptibility to infections, particularly by encapsulated organisms. The defective opsonization, abnormal alternate pathway of complement fixation, abnormal immunoglobulin and cell-mediated immunity all contribute to the vulnerability of these patients. Table 2 lists pathogens of concern in the infected patient with SCD for which antimicrobial therapy should minimally cover.

Table 2. Potential Pathogens in Patients with SCD by Type of Infection

Type of Infection	Microbes	Broadened Coverage
Sepsis/Fever	Strep pneumo, H. influenza	Salmonella, Gram neg enterics
Meningitis	Strep pneumo, H. influenza	N. Meningitidis
Acute chest syndrome	Strep pneumo, Mycoplasma, Chlamydia	Legionella
Osteomyelitis/Septic Arthritis	Salmonella, S. aureus, Strep pneumo	
UTI	E. coli, other gram neg enterics	

All febrile episodes or suspicion of infections should be reason for immediate medical attention given the risk to these patients. As previously noted, patients with SCD may have elevated baseline inflammatory markers, but this should not minimize the concern of possible infection within the appropriate clinical context.

HEMATOLOGIC COMPLICATIONS

Patients with SCD may have a range in their baseline hemoglobin. It is a critical part of their care to know the baseline untransfused level to determine the urgency when drop in counts occur particularly during an acute illness. There are several mechanisms that can lead to worsening of baseline anemia in these patients that should be considered. Aside from the expected drop in counts that is associated with correction of a dehydrated state, a decrease of more than 2 gm/dL should prompt a thorough history and physical exam to determine if a more serious cause is leading to this worsening anemic state. Distinguishing the various causes of the drop in hemoglobin can often be determined by the history, exam and simple blood testing.

Aplastic Crisis-

This state of acute worsening anemia often presents in correlation with a febrile illness. It is commonly associated with parvovirus B19 and more common in children prior to developing immunity against the virus. Patients tend to have a transient red cell aplasia with an onset 5 days following the exposure. Again, the decrease reticulocyte count in the setting of worsening anemia is characteristic of this process.

Hyperhemolytic Crisis-

SCD is a chronic hemolytic anemia. However, there can be episodes of increase hemolysis that leads to worsening anemia. There are lists of causes that can lead to a hyperhemolytic crisis and should be evaluated in these patients which include drug exposures, delayed transfusion reactions, coexisting glucose-6-phosphate dehydrogenase deficiency with oxidant exposure, infection or during the evolution of a sickle cell pain event. This process is distinguished from the aplastic crisis in that patients have a reticulocytosis. Markers of hemolysis, lactate dehydrogenase and indirect hyperbilirubinemia, are increased beyond the patients' baseline values.

Organ Sequestration-

Sequestration events can also lead to rapidly, life-threatening low hemoglobin levels. Blood is trapped in the spleen, or rarely lung or liver, and leads to enlargement of the organ. This most commonly is seen during childhood but can occur in adults, particularly those with milder genotypes as they may retain splenic function later in life. This will be described later in further detail. Providers must remain mindful to look for this as a cause of worsening anemia as it may not always be apparent upon first presentation.

Alloimmunization/Autoimmunization-

Patients with SCD tend to require transfusion of red cell units for complications of disease. Some of these patients remain on transfusion programs for very severe complications of disease and often is an indefinite therapy. Therefore, a growing complication is the development of antibodies to red blood cell antigens that make identifying donor units a problem in this patient population and may limit ability to do future transfusions. Once patients develop alloimmunization, they are at increased risk for autoimmunization as well.

Iron Overload-

Indications for transfusion of red blood cell units to patients with SCD put them at risk for the complication of iron overload. Patients at risk are those who have many intermittent transfusions or those on scheduled chronic transfusion programs. The excess iron deposits in the liver, heart and endocrine organs that can lead to damage or overt failure over time.

SPLENIC COMPLICATIONS

Acute Splenic Sequestration Crisis-

This complication presents with the drop in hemoglobin and spleen enlargement. The splenomegaly may be painful. Labs show increase erythropoiesis by presence of nucleated rbcs and reticulocytosis. Patients with homozygous S tend to have this complication in childhood. However, it can occur in those with hemoglobin SC and sickle beta plus thalassemia during adulthood. Mortality tends to be higher in adulthood and that only increases further with recurrent episodes.

Hypersplenism, Splenic Infarction, Splenic Abscess-

Additional complications of the spleen are worthy of mention in patients with SCD. Hypersplenism can be an intermittent problem where the hyperactive spleen consumes white blood cells as well as platelets. Infarcts in the spleen can be quite painful and abscesses may present with fevers in addition to the other symptoms. All the complications of the spleen in SCD are cause to consider definitive therapy given the risks and patient discomfort that they cause.

NEUROLOGIC COMPLICATIONS

Neurologic complications of SCD are often related to the vasculopathy associated with the disease. Patients and parents should be educated on these complications so not take them lightly given the morbidity.

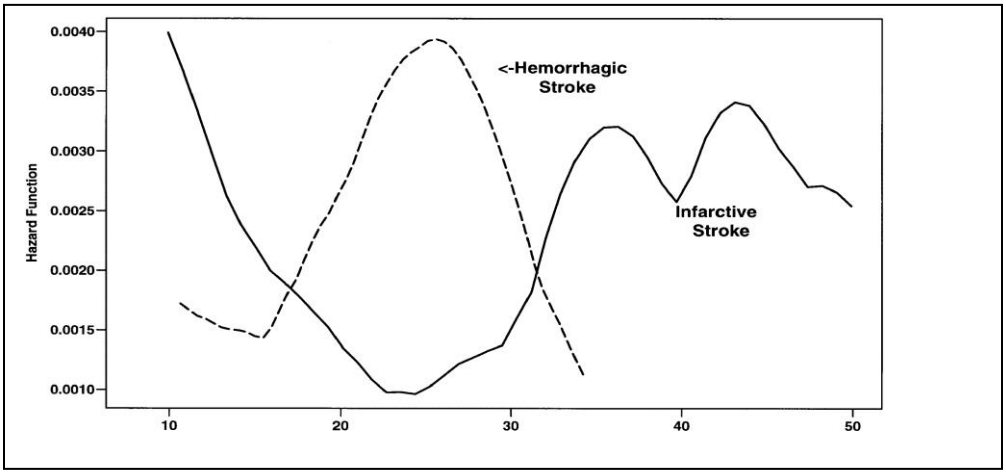
Headache-

One of the more common complaints presented by both children and adults with SCD is headache. Studies in children have documented the prevalence of recurrent headaches of 36% and migraines of 15% [8].

Cerebrovascular Accident-

Ischemic and hemorrhagic strokes are a serious complication in SCD with the majority occurring in those with hemoglobin SS disease.

Figure 6. Hazard rates of hemorrhagic vs. infarctive stroke



It is known children with SCD are at much higher risk than those without SCD to have stroke. The risk of stroke by age 20 years is 11% and increases to 24% by age 45 years [9]. Ischemic strokes are more common in those <20 years and again >30 years with hemorrhagic events more common between these ages (Figure 6).

Silent Cerebral Infarct-

Silent cerebral infarct (SCI) is a common neurologic finding in SCD where neuroimaging reveals cerebral lesions that are not associated with focal neurologic deficit. SCI can be found in children and adults but is a misnomer as these patients do have subtle cognitive and intellectual deficits. SCI has direct correlation with overt stroke [10].

OPHTHALMOLOGIC COMPLICATIONS

Several eye complications are described in SCD. Changes in the retina are commonly referred to as sickle retinopathy but can broadly be divided into non-proliferative and proliferative retinopathy with the basic mechanism of erythrostasis due to sickling. Patients with the hemoglobin SC tend to have some of the most severe manifestations of these eye disorders.

Non-proliferative Retinopathy-

These non-neovascular changes can be more subtle as it may not necessarily present with vision disturbance to the patient. It includes the following: retinal hemorrhage, changes in the macula and central artery occlusion [11].

Proliferative Retinopathy-

Neovascular disease is the leading cause of vision loss in patients with SCD and affects 10-20% of these patients [11]. These complications can be divided into 5 stages and listed on Table 3.

Table 3. Stages of Proliferative Sickle Retinopathy

Stage	Description
Stage I	Irreversible vascular occlusion in the peripheral retina
Stage II	Arteriovenous communications in the boundary between the vascular and ischemic retinas
Stage III	Presence of neovascularization formed from these anastomoses
Stage IV	Presence of vitreous hemorrhage
Stage V	Retinal detachment

CARDIAC COMPLICATIONS

The literature does not document any clear sickle cell specific cardiomyopathy. Many of the common findings such as cardiac flow murmur and cardiomegaly are often secondary to the chronic anemic state. Clinically, these patients tend to have complaints of fatigue and dyspnea. One pediatric study documents about 56% if their pediatric participants met the New York Heart Association Class I criteria [12]. This study also documented that electrocardiographic abnormalities were common findings but none were specific in this population [12]. A more recent study evaluating sudden death that occurs in SCD patients attributed the most common cause of cardiopulmonary death to the abnormal heart rhythm of pulseless electrical activity arrest [13].

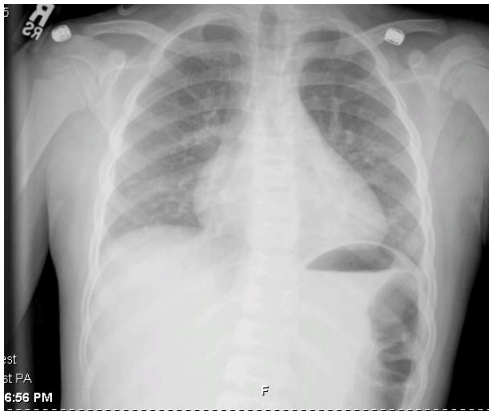
PULMONARY COMPLICATIONS

Pulmonary complications are a particular concern for the SCD patients as they are collectively very common and can lead to increase mortality. Often, patients present with hypoxia in the sick or well state and being able to differentiate the many causes can determine therapeutic interventions.

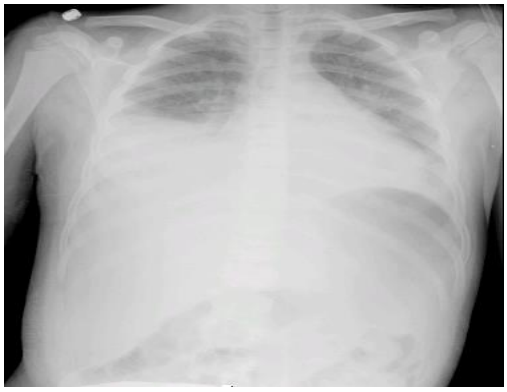
Acute Chest Syndrome-

Acute chest syndrome can be defined as the presence of respiratory symptoms, fever and associated radiographic changes representing a severe and often rapidly progressive inflammatory process in the lung (Figure 7). This syndrome can be triggered by many different causes and many times no infectious etiology can be found. As this is a potentially life-threatening complication of SCD, suspicion of acute chest syndrome should be reason to pursue prompt and thorough evaluation of the patient.

Figure 7. Chest x-ray of SCD patient with rapidly progressive acute chest syndrome



Admission Chest X-Ray



Chest X-Ray 12 Hours Later

Pulmonary Hypertension-

It is estimated that 6-11% of patients with SCD meet the diagnostic criteria for pulmonary hypertension which may carry association with increase mortality [14]. Studies are still determining the best means of evaluating and treating patients with SCD and suspicion of having pulmonary hypertension as there remains some heterogeneity in the patient clinical presentation and course.

Chronic Lung Disease, Obstructive Sleep Apnea, Pulmonary Emboli-

There are additional pulmonary complications that further complicate the health of patients with SCD. For example, these conditions may have a degree of overlap as recurrent acute chest syndrome can lead to chronic lung disease. Also, chronic pulmonary emboli can lead to pulmonary hypertension. The point of noting these complications is to impress that patients with SCD may have serious lung disease that warrants thorough evaluation and should not be dismissed as a normal part of their hematologic disorder. Lung complications may have effective therapies that once treated may improve symptoms and patient overall well-being.

GENITOURINARY COMPLICATIONS

Genitourinary and renal complaints are some of the early pathologic changes noted in SCD that may be overlooked as far as the impact on quality of life given some of the other life-threatening complications that have been described above.

Priapism-

Priapism is an unwanted, painful erection of the penis that is not necessarily related to sexual stimulation. There are two general types: (1) stuttering or (2) ischemic/prolonged. The long-term sequelae of these events may lead to irreversible damage resulting in erectile dysfunction. These events are not uncommon and has been documented that the probability for a male with SCD to experience priapism by age 20 years is 89% [15].

Enuresis/Nocturia-

The patient with SCD may have inappropriate urine concentrating ability due to damage in parts of the kidney early in life. This manifests as bedwetting, i.e. enuresis, or nocturia which is night awakening to urinate. It is clear that the prevalence of these issues in children and young adults with SCD is much higher when compared to unaffected individuals. That is, the prevalence of enuresis in children with SCD is 33% compared to 15% in the general pediatric population while the prevalence of nocturia was 79% in SCD patients [16]. These complications can lead to both patient and parent distress as it may not always be correlated with their SCD early on.

Chronic Kidney Disease-

Chronic kidney disease is the presence of kidney damage or decreased renal function for at least three months and is associated with increase morbidity and mortality in patients with SCD. Studies have shown that children and adults are both affected. Once present, patients tend to have shortened lifespan and increase in sickle cell specific complications [17].

HEPATOBILIARY COMPLICATIONS

Sickle hepatopathy is a broad category of liver complications that can occur in the patient with SCD. These are most often noted in patients with homozygous disease but can be seen in other genotypes.

Hepatic Crisis/Intrahepatic Cholestasis-

Hepatic crisis and intrahepatic cholestasis run along the same spectrum in the patient with SCD that have some similarities. Although more rare compared to gallbladder disease, they tend to present with extreme laboratory values that are quite concerning to the provider. In the case of hepatic crisis, patients have obstruction to sinusoids with rbc engorgement and sometimes mild centrilobular necrosis leading to transaminitis, tender hepatomegaly and jaundice [18].

Intrahepatic cholestasis is characterized by the same sinusoidal sickling leading to intracanalicular cholestasis that can cause a severe hyperbilirubinemia more so than with hepatic crisis [18]. The patient also has transaminitis and can have pain in the region of the liver but the distinguishing characteristic is the striking hyperbilirubinemia.

Hepatic Sequestration-

Like splenic sequestration, hepatic sequestration occurs when rbcs are trapped by the liver. This is much more a rare occurrence when compared to splenic sequestration. Similarly, rbcs can release from the liver and lead to the auto-transfusion phenomenon that is also seen in splenic sequestration. Therefore, patients are treated similarly.

Cholelithiasis, Hepatitis-

Due to the chronic hemolysis, patients tend to develop pigmented gallstones as early as childhood. Symptomatic gallstones and cholecystitis often require surgical intervention. Transmission of viral hepatitis from U.S. donor blood supply is uncommon at the present time. However, older patients with remote transfusion history, transfusion of blood products from regions of the world with high prevalence of viral hepatitis or strong clinical suspicion should have appropriate screening.

DERMATOLOGIC COMPLICATIONS

The predominant severe skin complication noted in patients with SCD is the recurrent leg ulcers that often have delayed or prolonged healing. These ulcerations can be quite severe and very painful to the patient. They can be debilitating to patients preventing their ability to ambulate. Effective therapies and prevention strategies of these ulcers remain difficult to define.

BONE COMPLICATIONS

Affected individuals with SCD are known to have characteristic findings on radiographic imaging that reflect the ongoing damage. A few are listed below.

Marrow Hyperplasia-

The chronic hemolytic anemia leads to erythroid hyperplasia and can be seen in the growth of the patient bone structure. This can be evidenced by frontal bossing or maxillary overgrowth noted in some patients.

Dactylitis/Bone infarct-

Dactylitis is the infarction of bones in the feet and hands resulting in an intense local inflammatory response in the tissue. This complication can be an early manifestation occurring in infants with exquisitely painful limbs. Along this spectrum is the bone infarct in other sites

and can occur at any age. Adult patients often present with the complaint of sickle cell pain that is more localized to a very specific site and not resolving in the usual manner with treatment. Swelling may or may not be present and imaging can sometimes reveal this as the inciting event.

Avascular Necrosis-

Ischemic necrosis occurring in the juxta-articular bone leads to this complication of SCD. Femoral and humeral heads are often common sites affected but other joints such as knees can also be involved.

Osteomyelitis-

Patients with SCD tend to be more susceptible to osteomyelitis which can be difficult to distinguish on radiographic imaging. These patients are at increased risk given the immune dysfunction previously described as well as the increase risk of infection of infarcted bone. Thorough evaluation and prompt treatment is recommended for these patients.

PAIN EVENTS

Pain is the most common cause for hospital admission in adults with SCD accounting for >90% of these encounters [19]. Pain in SCD can be difficult as there are no accurate measures other than patient report which often lead to the stigmatization of these patients. The types of pain can be variable occurring at any site and listed on Table 4.

Table 4. Classification of Pain in Sickle Cell Disease

- Acute-"crisis"
  - Tissue ischemia
  - ACS, priapism, dactylitis, hepatic crisis, sequestration
- Chronic
  - AVN, bone infarct, leg ulcers, chronic osteo, ill-defined intractable pain
- Mixed
- Neuropathic
- "Non-crisis"
  - Procedure related, traumatic, GI related (PUD/cholecystitis)
- Idiopathic

Despite the frequency of pain that brings the patient to seek medical attention, it has been observed that patients with SCD tend to experience more pain that what is captured by the healthcare system. This was documented in a longitudinal study where patient diaries revealed almost 55% of days were spent experiencing some pain and only 3.5% of those with "crisis pain" sought medical attention and 12.7% with "crisis pain" did not seek medical attention [20]. In addition, 29% of these patients had pain >95% of the diary days [20].

MULTIORGAN FAILURE SYNDROME

Acute multiorgan failure syndrome is the acute development of severe dysfunction of at least two of three major organs in the setting of a sickle cell pain episode [21]. These episodes seem to occur in patients who did not typically have a severe course at baseline. The pain event was unusually severe for that patient. The patient then progresses to a rapidly nearly fatal event that usually is associated with decrease hemoglobin, platelets and fever. It is suspected that this process may be the cause of death when patients die suddenly during acute pain episodes.

CONCLUSION

Sickle cell disease is a genetically and phenotypically heterogeneous disorder that poses severe complications to every organ system. Often, detailed history and examination is key in distinguishing SCD related diagnoses from other disease processes. Therefore, it is essential that clinicians approach care of these patients with broad differential diagnoses and keen awareness as these patients can encounter severe morbidity or mortality.

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