Osteonecrosis in Sickle-Cell Disease

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16.1 Introduction

Sickle-cell disease (SCD), an autosomal recessive disorder, is also called sickle-cell anemia (SCA) due to the hemolytic anemia characterized by abnormally shaped (sickled) red blood cells (RBCs), which are removed from the circulation and destroyed at increased rates, leading to anemia. Of greater clinical importance, the sickled RBCs cause vascular occlusion, which leads to tissue ischemia and infarction. The patients who are homozygous for the sickle-cell gene (hemoglobin SS) have a high risk of bone osteonecrosis [1–3] due to microvascular occlusion in relation to the disturbance in the erythrocyte architecture and the polymerization of hemoglobin S (in a deoxygenated state) producing cells that are crescent- or sickle-shaped with decreased deformability; the decreased deformability results in greater risk for clotting in small vessels. The incidence of osteonecrosis is also high in patients with hemoglobin SC (compound heterozygotes for Hb S- and Hb C-producing alleles: SC) and in the various types of sickle-beta-thalassemia (SThal) population. So, patients with sickle-cell disease often present with orthopedic disease manifestations requiring surgical intervention, with the most common indications being osteonecrosis and osteomyelitis. This article based on the experience of the authors treating more than 2,000 patients with SCD reviews the incidence of multifocal osteonecrosis in this disease, the distribution of the joints concerned by multifocal osteonecrosis, and the clinical consequences in the long term (average 15 years of follow-up) of multifocal osteonecrosis in these patients with sickle-cell disease and includes an approach to the medical and surgical management of patients with orthopedic complications related to sickle-cell disease.

16.2 History

This disease was unknown until the explanation of the sickle cells in 1904 by the Chicago cardiologist and professor of medicine James B. Herrick (1861–1954), whose intern Ernest Edward Irons (1877–1959) found "peculiar elongated and sickle-shaped" cells in the blood of Walter Clement Noel, a 20-year-old first-year dental student from Grenada; Noel was admitted to the Chicago Presbyterian Hospital in December 1904 suffering from anemia. Noel was readmitted several times over the next 3 years for "muscular rheumatism" and "bilious attacks." The first published paper of SCD [4] was therefore done by Herrick in 1910, who described the clinical and hematologic manifestations of the disease. Noel completed his studies and returned to the capital of Grenada (St. George's) to practice dentistry. He died of pneumonia in 1916 and was buried in the Catholic cemetery at Sauteurs in the north of Grenada. The disease was named "sickle-cell anemia" by Vernon Mason in 1922 [5]. As more cases began to surface, the mystery of just what this disease was only deepened. It was clear that for whatever reason, it occurred only or primarily in persons of African origin. In 1927, Hahn and Gillespie discovered that red blood cells from persons with the disease could be made to sickle by removing oxygen. Linus Pauling and colleagues were the first, in 1949, to demonstrate that sickle-cell disease occurs as a result of an abnormality in the hemoglobin molecule. This was the first time a genetic disease was linked to a mutation of a specific protein, a milestone in the history of molecular biology, and it was published in their paper "Sickle Cell Anemia." Two years later, in 1951, the famous Nobel Prize-winning chemist Dr. Linus Pauling and his colleague Dr. Harvey Itano discovered that the red, oxygen-carrying protein called "hemoglobin" had a different chemical structure in persons with SCD.

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This led Dr. Pauling [6] to coin the term "molecular disease" for disorders that resulted from proteins with abnormal chemical structures. Today, thousands of such diseases are known, but in 1951, SCD was the first. The details of the abnormality were worked out by Dr. Vernon Ingram [7] in 1956. In the 1970s, more details of how this abnormal structure affects the red blood cells were revealed, and better tests for the detection of the disease were developed.

16.3 Geography and Epidemiology

The origin of the mutation that led to the sickle-cell gene was initially thought to be in the Arabian Peninsula, spreading to Asia and Africa. It is now known, from evaluation of chromosome structures [8], that there have been at least four independent mutational events, three in Africa and a fourth in either Saudi Arabia or central India. These independent events occurred between 3,000 and 6,000 generations ago, approximately 70,000–150,000 years. The global distribution of Hb S is indicative of two factors: selection for carriers through their survival advantage in malaria-endemic regions and subsequent migration. Four region-specific African haplotypes (the Senegal, Benin, Bantu, and Cameroon haplotypes) and one Asian haplotype (the Arab-India haplotype) have been defined, providing support for the hypothesis that the mutation-causing Hb S has occurred, and been locally amplified, on at least two, and possibly several, separate occasions. In addition to the close geographic correlation between the frequency of the Hb S gene in populations and the historic incidence of malaria, evidence for the partial resistance of carriers to all forms of *Plasmodium falciparum* malaria [9] has been reported in many populations. The prevalence of sickle-cell disease is highest in sub-Saharan Africa. Although the scarcity of diagnostic facilities means that precise data are not available, a recent estimate suggests that it concerns 0.74 % of the births in sub-Saharan Africa. By comparison, approximately 0.15 % of the black population in the United States and Europe is afflicted with SCD. Sickle-cell disease is also an important cause of osteonecrosis affecting persons in the Indian subcontinent, in the Persian Gulf, in South America, in the Mediterranean countries and those from the Caribbean, and Central America. SCD is prevalent in other ethnic groups as well, including those from Mediterranean area countries as North Africa, Turkey, Spain, and Italy.

16.4 Basic Science of Sickle-Cell Disease

16.4.1 Molecular Genetics

The normal human hemoglobin molecule consists of four globin chains: two α chains and two ß chains. When α and ß chains are normal, this is abbreviated Hb A. The genetic basis of sickle-cell disease is a mutation on chromosome 11 that results in an amino acid substitution of valine for glutamic acid at the sixth position of the beta-globin subunit of hemoglobin. This results in hemoglobin S (Hb S). Diagnosis of the disease is confirmed by hemoglobin electrophoresis. Abnormal hemoglobin is designated by the type of abnormality in the globin chain. For example, the presence of one sickle-cell (S) ß chain and one C ß chain is abbreviated Hb SC. Homozygous sickle-cell disease is designated Hb SS. Abnormal hemoglobin, such as Hb SS, is usually the result of an abnormality in the ß (not α) chains. The term *sickle-cell disease* applies to all patients with at least a single Hb S chain and one other abnormal ß globin chain, which may be another sickle-cell ß chain (in which case the patient is homozygous Hb SS and by definition has sickle-cell anemia), Hb SC, or one of the thalassemias (Hb S-thal). Overall, Hb SS accounts for 60–70 % of the cases of sickle-cell disease in the United States and has the severest clinical manifestations of any of the sickle-cell disease variants. Sickle-cell trait (the heterozygous Hb SA, with one abnormal sickle gene designated S and one normal hemoglobin gene designated A) is a benign condition from an orthopedic point of view, with no propensity for vaso-occlusive complications, no osteomyelitis, and no osteonecrosis. Sickle-cell trait is however associated with an increased risk of a rare renal tumor, medullary carcinoma [10]. The importance of sickle-cell trait lies also with its implications for genetic counseling [8].

16.4.2 Anemia

The term sickle-cell disease is used to refer to all the different genotypes that cause the characteristic clinical syndrome, whereas sickle-cell anemia, the most common form of sickle-cell disease, refers specifically to homozygosity for the βS allele. In populations of African ethnic origin, sickle-cell anemia typically accounts for 70 % of cases of sickle-cell disease, with most of the remainder having hemoglobin SC disease (Hb SC disease) owing to the coinheritance of the βS and βC alleles. The third major type of sickle-cell disease occurs when βS is inherited with a β-thalassemia allele, causing Hb S/β-thalassemia. Sickle-cell anemia (SCA) is the most important syndrome of sickle-cell disease [11, 12]. This hemolytic anemia is characterized by abnormally shaped (sickled) red blood cells (RBCs), which are destroyed and removed from the circulation, leading to anemia.

16.4.3 Cellular Abnormalities in Sickle-Cell Disease

Hemoglobin S has a tendency to polymerize with relative ease in a deoxygenated state. This leads to a disturbance in erythrocyte architecture, producing cells that are crescent

or sickle-shaped in appearance and have decreased deformability. Factors that increase the rate of polymerization include high Hb S concentration, deoxygenation, lower pH, and a decrease in fetal hemoglobin (HbF). RBCs in SCA also appear to have an increased binding affinity for vascular endothelium [13, 14]. The degree of affinity correlates strongly with the severity of clinical disease. Several molecular interactions are likely to contribute to this endothelial affinity [15, 16]. One is a surface complex on reticulocytes that binds to endothelium. Another mechanism is a complex present on both reticulocytes and endothelium that binds thrombospondin (secreted by activated platelets).

16.4.4 Physiopathology of Osteonecrosis

Hb S is caused by a mutation in the β-globin gene. This mutation produces a hydrophobic motif in the deoxygenated Hb S tetramer that results in binding between β1 and β2 chains of two hemoglobin molecules [17]. This crystallization produces a polymer nucleus, which grows and fills the erythrocyte, disrupting its architecture and flexibility and promoting cellular dehydration, with physical and oxidative cellular stress.

16.4.5 Diagnosis and Screening

Diagnosis of sickle-cell disease is based on analysis of hemoglobin [18]. Typically, this analysis involves protein electrophoresis or chromatography, which are cheap techniques and widely available worldwide, although hemoglobin mass spectrometry and DNA analysis are being increasingly used because these techniques enable high-throughput testing. Antenatal screening is available to women in some countries to help to identify couples who are at risk of having a baby with sickle-cell disease and to offer prenatal diagnosis. Universal neonatal screening programs are established in the United States and England, with other programs being developed in Europe and Africa. Some of the improvement in survival in sickle-cell disease over the past few decades has been attributed to neonatal screening, facilitating early access to prophylaxis with penicillin, comprehensive care, and parental education on the early detection of complications such as acute splenic sequestration.

16.5 Frequency of Osteonecrosis

Multifocal osteonecrosis [19, 20] is the most common situation in SCD. It is defined as a disease of three or more anatomic sites. For example, a patient with osteonecrosis of one hip, one knee, and one shoulder would meet the criteria; a patient with three osteonecroses but not three separate sites involved would not be considered as multifocal osteonecrosis (e.g., two hips and one knee). Multifocal osteonecrosis is very frequent in SCD. For example, in a series of 200 patients with sickle-cell disease with a follow-up of 15 years [21], the occurrence of osteonecrosis was 158 lesions of the proximal femur associated with 151 proximal humerus osteonecroses, 33 lateral femoral condyle osteonecroses, 28 distal femoral metaphysic osteonecroses, 27 medial femoral condyle osteonecroses, 23 tibial plateau osteonecroses, 21 upper tibial metaphysic osteonecroses, and 14 ankle osteonecroses. The total number of osteonecrosis was 455 in these 87 patients. The epiphyseal lesions were more frequent than the metadiaphyseal lesions excepted in the proximal tibia. This means that in patients with hip osteonecrosis, the other joints [22] should be evaluated with radiograph and MRI if the joint is symptomatic. In reverse for patients with osteonecrosis of the knee, shoulder or ankle, the patients' hip should be evaluated by radiographs or MRI, regardless of whether the hip is symptomatic.

16.6 Natural Evolution and Consequence of Hip Osteonecrosis in Children

The contribution of synovial fluid to epiphyseal nutrition may offer some protection against infarction in children, among whom there is a lower prevalence of that complication (27 %) than in adults [23, 24].

16.6.1 Epiphyseal Infarction

Frequently, initial radiographs appear normal, and the earliest signs of avascular necrosis are seen on MR images (in particular, T2-weighted inversion recovery images), which show regions of high signal intensity indicative of bone marrow edema. Often, a serpiginous double line that consists of a hyperintense inner border and hypointense periphery can be seen at T2-weighted imaging. The "double line" sign results from the high-signal-intensity inflammatory response of bone with granulation tissue, inside the low-signal-intensity reactive bone interface. As osteonecrosis progresses, changes become evident at radiography. Early radiographic signs include lucency and sclerosis within the epiphysis; subsequently, crescent-shaped subchondral lucencies develop; and eventually, depression of the articular surface, collapse, and fragmentation occur.

16.6.2 Growth Plate

The effects of sickle-cell anemia on growth are thought to result from bone infarction. Epiphyseal shortening arises from vascular compromise, which causes damage to the growth plate, slowing or halting cartilage growth and leading to shortened bone. Premature fusion of growth plates often

occurs centrally because of the ingrowth of metaphyseal vessels. Epiphyseal deformities [23] with cupping of adjacent metaphyses have been described in sickle-cell anemia but also may occur in other childhood disorders, such as infection [24].

16.7 Natural Evolution and Consequence of Hip Osteonecrosis in Adults

The description of hip osteonecrosis was reported in the 1960s [25]. The prevalence of osteonecrosis in patients with sickle-cell disease is as high as 37–50 %. Osteonecrosis most commonly occurs in the humeral and femoral heads, due to their limited arterial network, which can easily succumb to occlusion by sickled cells. In both the hip and shoulder joints, the disease is bilateral in approximately 30 % of patients.

16.7.1 Symptomatic Hip Osteonecrosis

Extensive reports [26, 27] on the natural history of the symptomatic hip with osteonecrosis of the femoral head in adults with sickle-cell disease have been reported. Collapse of the femoral head [28] tends to occur early and at a high rate within 5 years after the diagnosis. No significant risk factors that could cause collapse, such as stage or size, were identified possibly because the rate of collapse was so high. This finding suggests that conservative operative procedures should be instituted early to try to prevent a poor outcome in hips with stage II disease.

16.7.2 Asymptomatic Hip Osteonecrosis

The same authors reported their evaluation of asymptomatic hip osteonecrosis [28]. The unfavorable outcome for most patients with an asymptomatic hip and osteonecrosis of the femoral head in the contralateral hip related to sickle-cell disease suggests that careful screening of the asymptomatic hip should be performed on a regular basis. They recommend that the asymptomatic hip be screened at 6-month intervals after presentation of the symptomatic hip, particularly when the volume of the osteonecrosis is large and when there has been collapse of the contralateral hip, because these two factors have been found to be associated with the rate of clinical and radiographic progression in the asymptomatic hip in patients with osteonecrosis of the femoral head associated with corticosteroid use or alcohol abuse. They also recommend evaluating the patient as soon as possible after the onset of pain because symptoms always preceded collapse. The intervals between the onset of pain and collapse may be as short as 3 months, and in the present study, the mean time between pain and collapse was only 35 months.

16.8 Preoperative Evaluation and Management

The complication rate for patients with sickle-cell disease undergoing orthopedic procedures is significantly higher [29, 30] than that for patients without sickle disease undergoing similar procedures, and these patients are more likely to have an extended inpatient hospital stay. Optimal perioperative management with a multidisciplinary approach should decrease the overall morbidity of these patients.

16.8.1 Preoperative Transfusion

The medical status [31] and attempts to prevent medical complications should be monitored by a specific medical team who has experience in preoperative management of patients with SCD undergoing orthopedic procedures [29]. We have experience of management of surgical procedure and medical complications of 2,300 patients with SCD. Part of the routine evaluation of patients with sickle-cell disease should include laboratory tests consisting of serial hemoglobin, Hb S%, renal function, liver function, and oxygen saturation. Based on these laboratory tests, the need for preoperative transfusion can be determined. All patients had a preoperative evaluation including hematologic consultation. Given the frequency of antigen mismatch between mostly Caucasian donors and African-origin recipients and in an attempt to prevent alloimmunization, we used, since 20 years, blood products which are phenotypically typed for ABO, Rhesus (Cc, D, Ee), and Kell. All the patients have antibody screening before surgery. The donor registry for the entire country is used as a resource when necessary. Red blood cell exchange to decrease the hemoglobin S level to less than 30 % was not performed before surgery except for 25 patients with a history of severe acute chest syndrome or a previous cerebrovascular episode or a severe anemia with hemoglobin less than 5 g/dL. For the other patients, acute simple transfusions were performed during and after surgery to maintain a level of hemoglobin between 8 and 10 g/dL. There is a general trend toward a conservative rather than aggressive transfusion regimen [32]. By adopting a simple transfusion therapy, transfusion-related complications in patients are decreased. All the patients had oxygen saturation during 3 days and were managed with anticoagulants postoperatively for 1 month when THA and only 1 week when core decompression.

16.8.2 Prevention of Infection

We prevent infection before, during, and after surgery. All patients with gallbladder stones had their gallbladder removed before hip surgery because gallbladder infection is a major source of secondary bone infection. Antibiotics

(first- and second-generation cephalosporins; 2.5 g per day) were administrated during and after surgery (3 days). Furthermore, all the patients had their implants fixed with cement containing antibiotics (Palacos Genta). Patients had surgery only when white blood cell count, erythrocyte sedimentation rate, and C-reactive protein values were within normal limits (according to the disease). According to the frequency of osteomyelitis in SCD, intraoperatively aspirates, smears, and excised specimens were collected before antibiotic administration and cultured for growth of aerobic and anaerobic bacilli. Histologic sections were examined for evidence of bacterial infection. After the operation, the antibiotics were continued for 3 days if intraoperative cultures were negative and for 1 month if the cultures or histologic examination were positive.

16.9 Intraoperative Management

Since there is a constant need for meticulous control of oxygenation and fluid hydration, general anesthesia [33] often is administered for these patients during orthopedic procedures. The most common intraoperative complications are excessive blood loss (53 %), followed by hypothermia (11 %). Therefore, patients require extensive monitoring of cardiac rhythm, blood pressure, temperature, and oxygen saturation. They also need active intraoperative warming, which usually consists of a combination of a warming blanket, humidifier, and blood/fluid warmer.

Patients with sickle-cell disease tend to contain latent Staphylococcus and Salmonella organisms in the infarcted bone due to the frequency of osteomyelitis in childhood. To identify latent infection and determine appropriate antibiotic therapy, culture of the femoral head bone chips and histology of all surgical specimens should be obtained during THA.

16.10 Postoperative Management

Postoperative management consists of intravenous hydration, supplemental oxygen, intravenous antibiotics, chest physiotherapy, and incentive spirometry. Common complications encountered in the early postoperative period include acute chest syndrome, vaso-occlusive crisis, and, less commonly, neurological and renal events.

16.10.1 Acute Chest Syndrome

Acute chest syndrome [34, 35] is characterized by some combination of respiratory symptoms, pain in the thorax or abdomen, fever, an abnormal chest exam, and eventual development of an infiltrate on chest radiograph. Although there is great variability in outcome, acute mortality is a risk. Furthermore, acute chest syndrome is a major risk factor for chronic lung disease. The etiology of this syndrome is a complex interplay of cruoric and/or fat embolism, infection, and in situ microvascular plugging by sickled red cells. Acute chest syndrome has a multifactorial etiology that includes rib infarction [36], infection, pulmonary infarction, and fat embolism. The pathophysiology of acute chest syndrome in sickle-cell disease is due to regional hypoxia leading to vasoconstriction. This results in increased polymerization of Hb S that leads to greater sickling and endothelial activation, with subsequent occlusion of the pulmonary vasculature. This triggers intrapulmonary shunting, which worsens the desaturation. Risks are increased in certain orthopedic procedures, particularly those that involve intramedullary canal reaming of long bones, by increasing the risk of fat embolism. Treatment of acute chest syndrome consists of hemoglobin levels, blood cultures, arterial blood gases, chest radiograph, spiral computed tomography scan of thorax, and exams to rule out pulmonary embolism and deep vein thrombosis. Treatment consists of blood transfusions, supplemental oxygen, adequate pain management, and empirical antibiotics (cephalosporin and macrolide).

16.10.2 Vaso-occlusive Crisis

Vaso-occlusive crisis, experienced by approximately 9 % of patients with sickle-cell disease, is defined as nonsurgical pain lasting >24 h and requiring opioid analgesia. Standard treatment consists of administering continuous IV opioid drug, typically morphine.

16.10.3 Transfusion-Related Complications

Due to large transfusions, patients may develop complications such as new alloantibody formation and immediate or delayed hemolytic reaction. As previously discussed, these complications are more often seen in patients who receive aggressive transfusion regimens.

16.10.4 Thromboembolic Prophylaxis in Sickle-Cell Disease

Little data exist about the risk of thromboembolic events in patients with SCD after THA and the best prophylaxis. Risk factors associated with venous occlusion include activation of the clotting cascade that can facilitate thrombus formation and hyperviscosity as a complication of transfusion [37]. Thrombin induces endothelial retraction resulting in the exposure of proadhesive extracellular components. It also upregulates endothelial expression of P-selectin, which increases binding among platelets and endothelial cells. Our experience with more than 600 patients with THA or revision of THA in SCD has only four documented deep vein

thrombosis and/or one documented nonfatal pulmonary embolism. All the patients had a prophylactic anticoagulant for 1 month postoperatively without any routine screening procedure (such as Doppler). Thromboembolism did not appear as a clinical problem in this population of patients. With warfarin, the frequency of hematoma was higher than with low-molecular-weight heparin (HPBM). The problem with HPBM is the risk of thrombocytopenia. In sickle-cell disease, platelets do not contribute to the pathophysiology of microvascular arterial occlusion. However, due to splenic sequestration, patients with sickle-cell disease often have thrombocytopenia. Although it occurs very rarely in adulthood, splenomegaly may be present and induce thrombopenic hypersplenism. After surgery, the high hematopoietic activity and the inflammatory response may induce noticeable thrombocytosis. We did not observe complications related to HPBM such as thrombopenia.

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