

Sickle Cell Disease - What you should know

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Sickle Cell disease (SCD) is an autosomal recessive genetic disorder of hemoglobin that causes red blood cells to sickle, which in turn causes vaso-occlusive organ infarcts, acute chest syndrome (ACS) and ultimately, premature death.^{1,2} The defect responsible for SCD is a single amino acid substitution (valine for glutamate) in the beta subunit of hemoglobin (Hb) that results in a mutation that facilitates polymerization of the subunit and sickling of the cell under certain conditions (hypoxia, hypothermia, dehydration and others). These deformed cells plug small vessels resulting in segmental organ ischemia and necrosis. The prevalence of SCD in African infants is 3 per 1000 live births. It also occurs in children of Mediterranean and Middle Eastern backgrounds. Genetic variants of SCD include homozygote Hb SS (sickle cell disease) and heterozygote, Hb S combined with another hemoglobin types. In the latter case, heterozygote Hb AS, where Hb A is normal hemoglobin, is termed sickle cell trait. Trait occurs in 8% of the African population. Children with Hb AS live normal lives, have normal hemoglobin concentrations and most are unaware that they even have sickle trait until a laboratory test establishes the diagnosis. However there are a number of other heterozygote combinations of Hb S including Hb SC and Hb S- β thal (more common variants), and several rarer hemoglobinopathies including Hb SD (Punjab), and Hb S-O Arab that may sickle to varying degrees when triggers are introduced. Hb SC has a normal hemoglobin but may sickle. Thalassemia has two variants: β^0 which produces no β chains and β^+ which produces a reduced amount of β chain; with the former variant, the risk of sickling is similar to that of HbSS with the latter, normal β chains reduce the risk of sickling.

The Defect.

The defect in SCD results from a mutation on chromosome 11 resulting in the substitution of the non-charged and hydrophobic valine for the negatively-charged and hydrophilic glutamate on the Hb β subunit.¹ This substitution alters the charge on the Hb strand causing it to polymerize with another Hb strand in the presence of hypoxia and other triggers. In the deoxygenated state, Hb S polymerizes in long bundles of 14 strands that twist like a braid. This causes the red cell to change from its characteristic shape to a sickle shape that leads to a myriad of pathological sequelae including organ infarcts. The weak nature of the inter- β unit forces that distort Hb during hypoxia permits reversal of the sickling and the opportunity to prevent the sickling with other treatments.

Diagnosis.

SCD is diagnosed at birth using hemoglobin electrophoresis. In the US, neonatal screening tests include a test for SCD for every live birth. The distribution of Hb in

sickle disorders varies; in SCD, 100% of the cells contain >75% Hb S. In sickle trait, the Hb AS cells contain 25-35% Hb S. Hence, when the cells are lysed and the hemoglobin is assayed, an electrophoresis distinguishes each Hb type and quantifies them. This is the most accurate test to diagnose the sickle state.

Although SCD is present at birth, Hb F prevents clinical sickling during the first 6 months post-natal age. Thus, phenotypic manifestations of SCD (including death) are exceedingly rare. Once the infant is 6 months old, the Hb F concentration decrease and sickling begins to occur. Because the sickledex test requires the Hb to sickle, infants with SCD cannot be diagnosed with this test during the first six months after birth.

Pathophysiology.

Initiation of sickling has traditionally been understood to begin with the introduction of an insult (hypoxia, dehydration, hypothermia, acidosis) followed by the Hb response, sickling. The deformed red cells become more fragile with hemolysis (resulting in anemia) and a limited ability to traverse the small capillaries (resulting in vaso-occlusive crises). The normal life span of red cells (120 days) is reduced in SCD to 10% of normal (15 days). Such vaso-occlusive crises cause a cyclical propagation of the sickling process that occurs in bone, lungs, brain and many other organs that in turn, leads to the constellation of clinical findings including death.

In the recent decade though, our traditional understanding of the pathogenesis of sickling has come under intense scrutiny.^{1,2} We now believe that the sickling process actually depends on an interaction among red blood cells, the endothelium and plasma constituents, a far more complex process than heretofore appreciated. Vaso-occlusive events appear to result from inflammation, vascular endothelial abnormalities, platelets and activation of the coagulation cascade. The instability of sickle Hb releases intracellular iron, which interferes with the permeability of the cell membrane to cations. The loss of intracellular cations dehydrates the cells thereby precipitating irreversible sickling. Membrane phospholipid abnormalities and activation of the clotting cascade further deforms the red cells. Intravascular hemolysis decreases nitric oxide production, which causes endothelial dysfunction with manifestations as pulmonary hypertension, priapism and other end-organ effects. This much more complex sickling process opens avenues for the introduction of new preventative and therapeutic strategies for the future.

Clinical Course.

The natural history of HbSS is one in which one-third of those afflicted have a progressive disease with organ dysfunction and death, one-half have significant but less devastating disease and the remaining 16% have a slow but progressive course. For HbSS, the death rate is decreasing; in part, this is due to aggressive antibiotic/vaccine therapy in young children and in part, due to more recent therapies that have decreased complication rates.³ In part, the varied outcome depends on the persistence of certain Hb: ie., Hb F, Hb SC, and HbS β^+ have fewer complications than others.

The presentation of HbSS is characterized by anemia (Hb 5-9 g/dL), reticulocytosis (5-10%) and an abnormal red cell smear. The life span of the red cells is markedly

abbreviated as the deformed red cells are hemolyzed as they traverse the spleen and other organs (see above). The anemia is further exacerbated by acute splenic sequestration and possibly aplastic anemia. These children may require chronic blood transfusions that lead to an iron overload and the development of alloantibodies (Kell and Duffy antigens), the latter causing difficulty for further transfusions. Supplemental chronic folic acid and other vitamin treatments prevent the development of megaloblastic anemia.

Vaso-occlusive crises in SCD result from microvasculature occlusions in phalanges, long bones, chest wall and pelvis. Abdominal pain that is difficult to distinguish from acute surgical abdominal pain results from mesenteric vascular occlusions. Management includes heat, hydration and pain management.

Acute chest syndrome (ACS) in SCD is characterized by the presence of acute respiratory signs with chest radiographic evidence of an infiltrate in a lung segment.^{1,2} The presentation is variable with a constellation of pulmonary findings that range from self-limited to respiratory failure (15%) and death. Evidence suggests that early onset of ACS may predict more ACS throughout childhood and warrant more aggressive interventions to prevent complications.⁴ The etiology of ACS is variable (including infectious causes) and the treatment is therefore quite variable. Chronic transfusions and hydroxyurea appear to decrease the frequency of ACS. Nitric oxide also attenuates the acute process.

Additional complications that occur include pulmonary hypertension (after chronic ACS), stroke (7-13%), renal dysfunction and infection. Those with a history of a stroke are at great risk for a subsequent stroke; those who have had a “silent” stroke by age 6 years are at a 14-fold greater risk for an overt stroke.^{5,6} The etiology of stroke has been elusive; there is some evidence that nocturnal hypoxia and parvovirus B19 are independent predictors of (silent) stroke. It has been suggested that “at risk” individuals be monitored for the former and a vaccine developed to prevent the latter. Strategies that have been recommended to identify those at risk for a stroke include annual transcranial Doppler of the cerebral blood vessels up to age 10 yr with transfusion of high-risk children to 18 yr. To address the risk of overwhelming sepsis, children under 6 years of age should receive pneumococcal and other bacterial-specific vaccinations as well as penicillin prophylaxis.

Novel strategies.

In addition to chronic transfusions to correct sickle cell anemia, a number of supplementary strategies may be forthcoming. Hydroxyurea, which stimulates Hb F production in some susceptible children, has been introduced as a treatment for SCD.⁷ Additional treatments include membrane-active medications and anti-adhesion therapies. Stem cell transplantation may cure the child provided it is instituted before organ dysfunction occurs.

Anesthetic Considerations.²

Perioperative morbidity and mortality in children with SCD are greater than in non-affected children. A recent study showed that 7% of all deaths in children with SCD was related to surgery. Early studies suggested the perioperative mortality is as great as 10%

and morbidity 50% in children with SCD. Studies from the 1990's reported a 1% mortality, a 30% incidence of any complication and a 10% incidence of ACS. The variability in the incidence of complications appears to depend on the nature of the surgery (superficial versus invasive) and child factors (ie, age, ACS, hospitalizations).

Basic principles for managing these children include standard factors to avoid intravascular sickling (see above), pain control and monitoring. Adequate hydration not only prevents sickling but may also prevent renal dysfunction; a brief fasting interval after clear fluids (2h) and adequate parenteral fluid administration.

Transfusion of red cells to children with SCD is controversial, especially in minor surgery. On the one hand, transfusion corrects anemia, dilutes HbS and prevents complications (such as stroke). Simple transfusion to correct an anemia to 10 g/dL has been shown to be as effective as aggressive transfusion (in which the concentration of HbS was <30%) in preventing perioperative complications and associated with fewer transfusion complications. On the other hand, transfusions may cause alloimmunization, transfusion reactions, iron overload and infection.

In the case of minor surgery, a retrospective study of 34 children with SCD who underwent superficial, non-cavity surgery (excluding T&A surgery) experienced no serious perioperative complications from SCD.⁸ Although this was a small study and retrospective in design, it suggests that a prospective study should be undertaken to determine what if any, are the risks of not transfusing children with SCD who undergo minor surgery.

Currently, most children with SCD who undergo surgery require a simple transfusion to a Hb \geq 10 g/dL. Those who are heterozygote (HbSC) with a Hb \geq 10 g/dL and no SCD complications (ie., ACS) have no clear requirement for any preoperative treatment but those with complications, should have their concentration of HbS reduced. The risk of alloimmunization precludes family members from donating blood (future rejection of stem cell transplanted cells) and leukoreduction should be used with every unit of blood.

Anesthetic technique.

There is no ideal anesthetic for children with SCD. All anesthetics appear to be safe and regional anesthesia has been used extensively to treat and prevent complications. Any strategy that decreases flow in any vascular bed (hyperventilation, dehydration) should be avoided. Surprisingly, tourniquets have been used in children with both HbSS and HbAS up to two hours without serious complications. Cardiopulmonary bypass would be expected to cause sickling (with hypothermia, hypotension) although children with HbSS and HbAS have undergone bypass without transfusion and without complications. In most instances, aggressive exchange transfusion to decrease the HbSS concentration is recommended.

Safe management of children with SCD and other sickle hemoglobinopathies requires a high-level of collaboration among hematology, surgery and anesthesia. The morbidity

and mortality for children with SCD who undergo surgery should be relatively small. Attention to the usual standards for anesthetic practice will ensure a successful outcome.

References.

1. Firth PG. Anaesthesia for peculiar cells - a century of sickle cell disease. *Br J Anaesth* 2005; 95: 287-99
2. Haberkern C, Weibel NE, Eisses MJ, Bender MA. Essentials of Hematology. In: *A Practice of Anesthesia for Infants and Children*. Cote CJ, Lerman J, Todres ID (eds). Elsevier, Philadelphia, PA. Chapter 9, 2009
3. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. *Blood* 2004; 103:4023-7
4. Quinn CT, Shull EP, Ahmad N, et al. Prognostic significance of early vaso-occlusive complications in children with sickle cell anemia. *Blood* 2007; 109: 40-5
5. Mazumdar M, Heeney MM, Sox CM, Lieu TA. Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion. *Pediatrics* 2007; 120: e1107-16
6. Buchanan GR, DeBaun MR, Quinn CT, Steinberg MH. Sickle Cell Disease. *Hematology* 2004; 35-47
7. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; 122:1332-42
8. Fu T, Corrigan NJ, Quinn CT, et al. Minor elective surgical procedures using general anesthesia in children with sickle cell anemia without pre-operative blood transfusion. *Pediatr Blood Cancer* 2005; 45: 43-7