Austin Journal of Pediatrics

Austin Publishing Group

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Editorial

Sickle Cell Disease in 2014 – What's the Crisis?

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Received: May 27, 2014; **Accepted:** May 28, 2014; **Published:** May 30, 2014

Editorial

Sickle Cell Anemia (SCA) is caused by a well-characterized mutation in the beta-globin chain of Hemoglobin (Hb). This leads to an unstable Hb molecule that polymerizes in the deoxygenated state, leading to deformation of the Red Blood Cell (RBC). These abnormally shaped RBCs are less effective in oxygen transportation, cause occlusion of the small blood vessels, and have a significantly shortened survival, resulting in a chronic hemolytic anemia. The hemolytic process in SCA also results in the release of the intracellular contents of the RBC, leading to the depletion of intravascular Nitric Oxide (NO) and resultant vasoconstriction.

SCA is generally found in people of African descent, and is inherited in an autosomal recessive manner, with one affected beta-globin gene passed from each parent. Sickle cell trait occurs when only one sickle cell mutant chain is present; this may present as a mild anemia but is usually asymptomatic. However, when the other beta-globin gene is affected by another mutation, such as Hemoglobin C or beta-thalassemia, this can result in a compound hemoglobinopathy generally referred to as a sickle cell syndrome. Presentation of these syndromes is dependent on the nature of the different mutations, and ranges from minimally to highly symptomatic.

The complex pathophysiology of SCA leads to a highly variable clinical phenotype, and the severity of the manifestations may differ even between members of the same family. Patients have a chronic, and often well compensated, anemia, with intermittent signs of hemolysis such as jaundice and icterus . Vaso-occlusive symptoms can occur in any organ; bony pain crisis from skeletal ischemia is common, while stroke and acute chest syndrome may be the most devastating complications [1]. When hemolysis is more prevalent, symptoms of vasoconstriction such as priapism and pulmonary hypertension may predominate [2]. Splenic dysfunction due to infarction predisposes patients to bacterial sepsis with encapsulated organisms, and intercurrent viral illness may precipitate aplastic crisis.

The most important screening test for SCA is the complete blood count and peripheral blood smear, which should identify the chronic hemolytic anemia and the presence of abnormal RBC morphology. The Hb solubility test, commonly referred to as the Sickledex, is sensitive but not specific to SCA. Confirmatory testing demonstrates the presence of sickle Hb (Hb S) by separating the different Hb variants by molecular size and charge; commonly used modalities include electrophoresis and high purity liquid chromatography. Where available, molecular testing for genetic analysis may be helpful in characterizing compound hemoglobinopathies or when there is an unusual presentation or family history.

Many countries, including the United States and the United Kingdom, are now performing universal newborn screening for SCA. This stems from a study in 1986, which demonstrated that early penicillin prophylaxis for infants and children with SCA could prevent septicemia and death, with an 84% reduction in the incidence of infection [3]. In addition, timely neonatal diagnosis allows for enhanced parental education and the early initiation of appropriate and comprehensive clinical care, which will decrease the morbidity and mortality of SCA in childhood [4].

Management of SCA is individualized, and directed at the specific symptom complex of each patient. There are no good predictors of which patients will have high-risk disease. All patients should receive folic acid to support active hematopoiesis, and antimicrobial prophylaxis, as discussed above. Because of splenic dysfunction and risk of sepsis, they require prompt evaluation when febrile. Times of illness may also precipitate sickle cell crises, which may related to transient aplasia, hemolysis, or vaso-occlusion.

Initial management of sickle cell crisis includes supplemental oxygen to prevent further RBC sickling and intravenous hydration to decrease blood viscosity and improve blood flow [5]. Empiric antibiotics should be considered, especially when febrile. Appropriate analgesia is important, and these patients will often require narcotics for adequate pain relief.

Blood transfusion can provide normal RBC to improve oxygen transport to the tissues and decrease the proportion of Hb S in the blood, and is often helpful in managing a crisis. For more severe presentations, such as acute chest syndrome, exchange transfusion may be necessary [6]. This may be done manually or by automated erythrocytapheresis to acutely remove the sickled RBC and replace them with donor RBC to rapidly achieve aHb S level of less than 30%. When patients have a history of crises, they may require chronic RBC transfusion, given at a frequency that suppresses hematopoiesis to maintain the Hb S level below 30%.

Infectious diseases are much less of a concern with current pre-transfusion testing, but alloimmunization against RBC antigens occurs in up to one-third of patients receiving simple transfusion. An important risk of blood transfusion, especially in the setting of frequent or chronic transfusions, is iron overload, and excess iron can deposit in tissues leading most frequently to hepatic, cardiac, and endocrine dysfunction. Chelation of the excess iron will be required, and both subcutaneous and oral agents are available [7].

For patients with frequent or life-threatening crises, chronic management may be necessary. In 1998, Hydroxyurea (HU) was approved for use in adults with SCA, and the more recent HUSOFT

Citation: Stoffman JM. Sickle Cell Disease in 2014 – What's the Crisis?. Austin J Pediatr. 2014;1(2): 1007.

and HUG-KIDS studies demonstrated safety in children, with some evidence of clinical benefit. This antineoplastic agent was known to increase the production of fetal Hb (Hb F), thereby decreasing the proportion of Hb S and improving blood flow. More recently, there is evidence that it is beneficial in SCA by reducing white blood cells and inflammatory mediators contributing to endothelial damage and improving NO metabolism leading to decreased vasoconstriction [8,9].

The BABY-HUG study was a randomized controlled trial to evaluate HU in infants with SCA. Children were enrolled between 9 and 18 months of age, and the primary endpoints were markers of splenic and renal damage, as surrogate markers for end organ dysfunction. The study was unable to meet its primary endpoints, but did show a statistically significant improvement in hematological parameters and reduction in acute crises in the HU treated group. As a result, the investigators recommended HU for all children with SCA [10]. Unfortunately, HU use has been limited by concerns about efficacy, since SCA is not yet an approved indication and the risk-benefit ratio is uncertain. There is also the potential for carcinogenicity with long-term use and the impact on the family of regular use of a costly medication [11].

The only potential cure for SCA is Hematopoietic Stem Cell Transplantation (HSCT), which has been much more extensively investigated and used in beta-thalassemia. HSCT has been limited in SCA because of lack of information and experience, difficulty in identifying HLA-suitable donors, and risk of transplant-related toxicities [12]. Myeloablative HSCT regimens have a 95% success rate but with a high risk of complications, so non-myeloablative regimens have been developed with less risk of both acute and chronic complications, and clinical trials with this approach are ongoing [13].

Management of patients with SCA is best accomplished in the context of a comprehensive care program, staffed by a multidisciplinary team with interest and experience in patients with SCA. While this may not always be possible, it is important that individuals caring for patients with SCA are aware of the issues of acute and chronic management, as well as actively monitoring for the complications of both the disease and its treatment. New disease-modifying drugs for SCA are under development or in clinical trials, which have the potential to change the way we manage these patients in the future.

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Austin J Pediatr - Volume 1 Issue 2 - 2014
ISSN : 2381-8999 | www.austinpublishinggroup.com

Citation: Stoffman JM. Sickle Cell Disease in 2014 – What's the Crisis?. Austin J Pediatr. 2014;1(2): 1007.