Sickle Cell Disease in the Emergency Department

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KEYWORDS

• Sickle cell disease • Vaso-occlusive crisis • Acute chest syndrome
• Emergency department

KEY POINTS

- Early and aggressive pain management is a key priority in emergency department (ED) visits among patients with sickle cell disease (SCD).
- Emergency providers (EPs) must also actively seek to diagnose other emergent diagnoses (eg, acute chest syndrome) in patients with SCD and differentiate them from vaso-occlusive crisis.
- Administration of intravenous fluids must be based on patient volume status. The benefit of blood transfusions should be balanced against their impact on volume status and viscosity.
- EPs should be especially aware of cognitive biases that may misdirect the diagnostic process.
- Coordination of care with hematology is an important part of the effective ED and long-term management of patients with SCD.

INTRODUCTION

Emergency providers (EPs) practicing in North America must be familiar with sickle cell disease (SCD) and its complications. SCD is the most common genetic disease in the United States: 1 in 12 African Americans carry the autosomal recessive mutation, whereas 1 in 500 African Americans born has the disease.[1]

In SCD, hemoglobin (Hb) molecules have a propensity to aggregate into rigid polymers, particularly under conditions of low oxygen tension, resulting in the characteristic sickle-shaped erythrocytes that cause vaso-occlusion and ischemia.

The clinical hallmark of SCD is episodes of acute pain, and this is the most common reason for emergency department (ED) visits and inpatient admissions by patients with

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SCD.[2–6] In addition to managing these acute pain episodes, the EP must be alert to other manifestations, complications, and comorbidities of the disease, some of which carry significant risk for morbidity and mortality. In this article, the clinical presentations and management of SCD in the ED are described, and key decisions and current controversies are discussed.

HISTORY

SCD was first described in the Western medical literature by James B. Herrick in 1910.[7] In 1949, James V. Neel described the pattern of inheritance, with individuals who were heterozygous for the responsible gene having sickle cell trait (SCT) and homozygous individuals having SCD.[8] SCD was the first human anemia defined at the amino acid level.[9]

PATHOPHYSIOLOGY

Human Hb molecules are typically tetramers comprising 4 subunit proteins (2α and 2β subunits).[10] The exact composition of the peptide chains determines the specific shape into which the molecule can fold. HbS is the result of a glutamic acid to valine substitution at the β_6 amino acid position.[11,12] The result is polymerization caused by a hydrophobic interaction between the altered, deoxygenated molecule and other Hb molecules.[11] As a consequence, there is a change in the shape and reduction in the critical ability of erythrocytes to deform.[11,12] Although it was initially believed that the ensuing change in flow characteristics and erythrocyte aggregation alone caused vaso-occlusion, the root cause is multifactorial. Initial endothelial activation with increased adhesion of erythrocytes and leukocytes is followed by formation of heterocellular aggregates, which physically result in occlusion and local hypoxia. This process triggers a vicious cycle of increased HbS formation caused by hypoxia, presence of inflammatory mediators, free radicals, and reperfusion injury. Hb also binds nitric oxide (NO), a potent vasodilator, and releases it with oxygen.[10] Ineffective binding and release of NO along with hemolysis and erythrocyte lysis further reduce NO production and result in persistent tissue hypoxia.[10,13] Erythrocytes are more likely to sickle and become rigid the more dehydrated they get. This process is in large part caused by changes in cation homeostasis, specifically, increased potassium and water efflux mediated by potassium-chloride cotransport and Gardos channels (Ca^{++} dependent K^+ channel) (**Fig. 1**).[11,14]

SCD is commonly represented by the primary HbSS genotype. There are also 5 other genotypes that are associated with varying clinical severity, and all have most of their Hb as HbS.[13] HbSS, commonly referred to as sickle cell SS disease, is the most severe clinically, with the heterozygous HbS/β^o thalassemia genotype being similarly severe. HbSC has intermediate severity, HbS/β^+ has mild to moderate severity, and HbS/HPFH (hereditary persistence of HbF) and HbS/HbE show mild to no symptoms.[14] There exist several other genotypes that are exceedingly rare but do cause disease of varying severity. Those with SCT (heterozygous with HbA) have Hb that is majority HbA (**Table 1**).[13]

EPIDEMIOLOGY

It has been known for more than 60 years, based on geographic distribution and genetic studies, that the sickle cell gene provides protection against malaria infection by *Plasmodium falciparum* in heterozygotes.[15] However, the mechanism of this protection is only now being elucidated. It is theorized that the presence of HbS inhibits