Sickle Cell Disease in Sub-Saharan Africa

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KEYWORDS

• Sickle cell disease • Children • Public health • Bacteremia • Sub-Saharan Africa

KEY POINTS

- Sickle cell disease is a common and growing health problem in many parts of sub-Saharan Africa (SSA), where at least 240,000 affected children are born with the condition every year.
- Sickle cell disease is widely neglected on the continent, where an estimated 50% to 90% of those born with the condition die undiagnosed before their fifth birthdays.
- An unknown, but probably large, proportion of these deaths are almost certainly attributable to 2 main conditions: malaria and invasive bacterial infections.
- With economic and public health advancements in many parts of the region, survival of affected children is likely to improve, which will lead to a growing need for appropriate medical services.
- A greater emphasis on basic and applied research in the area of sickle cell disease in SSA could lead to substantial improvements to the lives and livelihoods of millions of affected people and their families.

INTRODUCTION

Sickle hemoglobin (HbS) is a structural variant of normal adult hemoglobin (HbA; $\alpha_2\beta_2$) in which the normal beta-globin subunit is replaced by a mutant form of the molecule (β^S) in which the glutamic acid residue normally present at position 6 is replaced by a valine residue, the result of a single nucleotide polymorphism (thymine to adenine; rs334) at position 17 of the *HBB* gene.[1] This abnormal HbS polymerizes reversibly under low oxygen tension, and alterations to the shape, rheological properties, and membrane properties of the red blood cells that result from these

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polymerization events are central to the pathophysiology of the resultant disease.[2] The term sickle cell disease (SCD) refers to a heterogeneous group of conditions in which HbS predominates. The most common form of SCD results from the homozygous inheritance of the β^S mutation, a condition most commonly referred to as either HbSS or sickle cell anemia (SCA). Although SCA is responsible for at least 70% of SCD globally,[3] SCD can also result from compound heterozygosity for HbS in association with a wide range of other *HBB* mutations, including the mutation that results in the production of another structural variant, hemoglobin β^C (HbSC) and one of the many β-thalassemia mutations that lead to the reduced production of normal beta-globin (HbS/β-thalassemia).[4] Although the geographic range of HbS extends throughout most of sub-Saharan Africa (SSA) north of the Zambezi river, both HbC and β-thalassemia are confined to more limited parts of West Africa and to the historic trade routes of North Africa. As a result, HbSS is by far the most significant form of SCD in SSA, and the form of SCD about which most is known. HbSS is therefore the main focus of this article.

ORIGINS OF THE SICKLE MUTATION

Haplotype analysis suggests that the rs334 allele that encodes for β^s has arisen, and been independently amplified to its current population frequencies, on at least 2 and likely more occasions.[5,6] Despite being detrimental in its homozygous form (HbSS) the rs334 allele has reached high population frequencies throughout much of SSA to the extent that through much of the continent more than 15% of the population are heterozygotes (HbAS; sickle cell trait), and notably more than twice that in small surveys from selected populations.[7] That such high heterozygote frequencies might result from selection for HbAS through a survival advantage against malaria was first suggested more than 6 decades ago[8] and, despite some early skepticism, this hypothesis has since been confirmed beyond any reasonable doubt (reviewed in Ref.[9]). In a recent meta-analysis of available data from 44 studies conducted throughout the continent, Taylor and colleagues[10] estimated that children with HbAS are more than 90% less likely to develop severe and complicated *Plasmodium falciparum* malaria, the form of malaria associated with the most deaths, than normal children with HbAA. This conclusion has recently been reaffirmed in the most substantial study of its kind conducted to date, involving almost 12,000 children with severe malaria and more than 17,000 controls recruited from 12 sites throughout the malaria-endemic world, in which the odds ratio (OR) for severe malaria among HbAS children was 0.14 and was associated with a significance level rarely seen in such studies ($P = 1.6 \times 10^{-225}$).[11] Moreover, the effect of HbAS is not limited to the most severe forms of malaria but also extends to protection against uncomplicated forms of the disease,[10] with the result that HbAS confers even wider health benefits and survival advantages by protecting against the longer-term consequences of uncomplicated malaria, such as chronic anemia,[12] malnutrition,[12,13] and invasive bacterial infections.[14,15]

The precise mechanism by which HbS protects against malaria remains a subject of some speculation. Early work suggested that erythrocytes containing HbS might be less supportive of *P falciparum* growth and multiplication than normal red cells under low oxygen tension,[16–19] but more recently it has been suggested that HbS might protect against malaria by mediating the reduced display of the parasite-encoded protein *P falciparum* erythrocyte membrane protein-1 (PfEMP1) on the surface of malaria-infected erythrocytes.[20,21] The adherence of *P falciparum*–infected red blood cells