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Complications Associated with Sickle Cell Trait: A Brief Narrative Review

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ABSTRACT

Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30% to 40% in sub-Saharan Africa. Long considered a benign carrier state with relative protection against severe malaria, sickle cell trait occasionally can be associated with significant morbidity and mortality. Sickle cell trait is exclusively associated with rare but often fatal renal medullary cancer. Current cumulative evidence is convincing for associations with hematuria, renal papillary necrosis, hyposthenuria, splenic infarction, exertional rhabdomyolysis, and exercise-related sudden death. Sickle cell trait is probably associated with complicated hyphema, venous thromboembolic events, fetal loss, neonatal deaths, and preeclampsia, and possibly associated with acute chest syndrome, asymptomatic bacteriuria, and anemia in pregnancy. There is insufficient evidence to suggest an independent association with retinopathy, cholelithiasis, priapism, leg ulcers, liver necrosis, avascular necrosis of the femoral head, and stroke. Despite these associations, the average life span of individuals with sickle cell trait is similar to that of the general population. Nonetheless, given the large number of people with sickle cell trait, it is important that physicians be aware of these associations.

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Sickle cell trait is characterized by the inheritance of a normal hemoglobin gene (HbA) from 1 parent and an abnormal, mutated β_1-globin gene, the sickle hemoglobin gene (HbS), from the other parent.[1] In sickle cell disease, 2 abnormal allemorphic hemoglobin genes are inherited, of which at least 1 must be the sickle hemoglobin. In the homozygous sickle cell disease (HbSS), both abnormal hemoglobins are HbS. A normal adult hemoglobin is made from a combination of 2 β-globin protein chains with 2 α-globin chains and heme. The β_1-globin gene is located on the short arm of chromosome 11. Approximately 150 diseases have been linked to this same chromosome 11.

The sickle gene is multicentric in origin, and 4 main haplotypes, representing 4 different mutations, have been identified.[2] The Asian (Arabo-Indian) haplotype is thought to have originated in Central India or Saudi Arabia, the Benin haplotype originated in central West Africa, the Senegal haplotype originated in the West African region above the Niger river, and the Bantu (or CAR) haplotype originated in central and south central Africa. The haplotypes influence sickle cell disease severity. The Senegal haplotype, on average, is associated with the least severe disease, and the Bantu haplotype is associated with the most severe disease.[2] The influence of these haplotypes on complication rates in individuals with sickle cell trait is yet to be determined.

It is estimated that 300 million people worldwide carry the sickle cell trait, with the highest concentration in Africa and the Mediterranean region. Approximately 1 in 3 persons in West Africa and 1 in 5 persons (20%) in the eastern province of Saudi Arabia carry the sickle cell trait.[3,4] In the United States, the prevalence of sickle cell trait is estimated

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at approximately 8% in African-Americans and 0.05% in white Americans. Data from the newborn screening program in California suggest the incidence of sickle cell trait is approximately 7.9 per 100,000 newborns.[5]

Sickle cell trait can coexist with gene deletion α-thalassemia, particularly in blacks. There is a trimodal distribution of HbS levels in individuals with sickle cell trait, based on the number of α-globin genes. Individuals with sickle cell trait and normal α-globin genotype have approximately 40% HbS in their erythrocytes, whereas those with loss of 3 α-globin genes have 20% to 25% HbS. Those with loss of 1 α-globin gene (_α/αα genotype) have 35% HbS.[6]

Increased red blood cell sickling and polymerization can occur in sickle cell trait under conditions of severe tissue hypoxia, acidosis, increased viscosity, dehydration, and hypothermia. The severity of polymerization decreases in those with lower HbS concentration. In vitro studies have established that heterozygous sickle cell trait erythrocytes sickle when the oxygen level is decreased to 2% compared with 4% to 6% for homozygous erythrocytes.[7] The mean percentage of reversible sickling for sickle cell trait in military recruits who exercised to exhaustion in simulated elevations increased from 2% at elevations of 4050 ft to 8.5% at elevations of 13,123 ft.[8] At 0% oxygen saturation, approximately 35% of sickle cell trait cells sickle compared with 70% for HbSS.[9]

Traditionally, sickle cell trait has been viewed as a benign condition, a non-disease, partially protective against falciparum malaria and without any of the painful episodes characteristic of the homozygous sickle cell disease.[10,11] On a population basis, sickle cell trait has no discernible impact on life expectancy.[12] Hemoglobin and hematocrit values in individuals with sickle cell trait are similar to those of persons without hemoglobinopathy.[11,13] Individuals with sickle cell trait are eligible for blood donation in the United States and in many other countries.[14,15] The storage quality of sickle cell trait blood is good and comparable to that of HbAA blood.[16] However, current leukocyte-reduction filtration systems tend to be clogged by blood from sickle cell trait donors.[17]

Sickle cell trait is not completely benign. There is extensive literature describing the morbidity of sickle cell trait.[11] Much of the data were derived from case reports or uncontrolled observational studies. To attribute a specific complication to sickle cell trait, at a minimum, it must occur in greater frequency in individuals with sickle cell trait than in the general population. On the basis of the strength and specificity of observed associations with sickle cell trait, the complications can be grouped as definite, probable, or possible (Table 1). It is important that both physicians and persons with sickle cell trait become familiar with these potential complications so that prompt treatments can be offered when they occur, and preventive steps can be taken when and where appropriate.

CLINICAL SIGNIFICANCE

- Sickle cell trait is found in approximately 300 million people, with concentrations in Africa, the Arabian Peninsula, India, the Mediterranean, and the southern United States.
- Although largely a protective carrier state, sickle cell trait is associated with rare but fatal renal medullary cancer, exercise-related deaths, splenic infarction, hematuria, hyposthenuria, venous thromboembolism, complicated hyphema, and fetal loss.
- Knowledge of these associations is critical for appropriate management.

DEFINITE ASSOCIATIONS

Renal Medullary Carcinoma

Renal medullary carcinoma is a rare, aggressive tumor of the kidney that is seen almost exclusively in young individuals with sickle cell trait. It was first described in 1995 in a case series report of 34 patients, 33 of whom had sickle cell trait.[17] Approximately 120 cases have been reported to date.[18] Of these, only 1 patient is known not to have a positive sickling status. All patients except 1 were aged less than 40 years, with a median age of 22 years. There is a male preponderance (M: F of 3:1) before age 24 years and equal frequency by gender after age 24 years.

The tumor arises from the epithelium of distal collecting ducts and grows in an infiltrative pattern, invading the renal sinuses. Most of the tumors are found in the right kidney (3:1 comparing right with left kidneys). The tumor tends to be lobulated, firm, and poorly circumscribed. Cytology consists of a primary cohesive group of cells with vacuolated cytoplasm, displaced or indented nuclei, and prominent nucleoli. The tumor demonstrates lack of chromosomal imbalance and has distinct molecular signature compared with renal cell cancer. In 1 case, chromosome 11, the same chromosome that carries the β-globin gene, was monosomic in all cells analyzed. Beckwith-Wiedeman syndrome and multiple tumor-associated chromosome region 1, similarly localized to chromosome 11p15.5, are associated with renal cancer.

Hematuria and flank pain are the most common initial symptoms. Most tumors can be detected with computed tomography or magnetic resonance imaging. In almost all patients, the disease is disseminated at the time of diagnosis. The median survival is approximately 15 weeks. Only 3 patients appear to have survived the disease, with the longest reported survival of 8 years. Management options include radical nephrectomy, chemotherapy using regimens for transitional and renal cell carcinomas, and palliative radiation therapy.[19]

Hematuria and Renal Papillary Necrosis

Hematuria, both microscopic and macroscopic, is the most frequent complication of sickle cell trait.[11,20,21] Hematuria accounted for 4% of hospitalizations for sickle cell trait in male