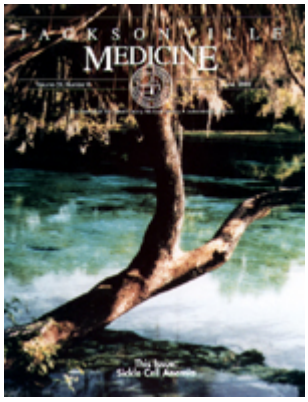

Morbidity Associated With Sickle Cell Trait

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Morbidity Associated With Sickle Cell Trait

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Sickle cell anemia is one of the first diseases to be understood at the molecular level. The amino acid valine is substituted for glutamic acid at the sixth position of the b-globin chain, due to a GAG to GTG codon mutation. The resultant sickle hemoglobin (Hgb S) has a unique tendency to aggregate and form long strands of rodlike polymers on deoxygenation, with the subsequent morphological changes limiting the red blood cells ability to traverse the microcirculation. Sickle trait (Hgb AS) red blood cells can also undergo polymerization with morphologic sickling at 0% oxygen saturation.[1,2] The amount of polymerization with complete deoxygenation is reflective of hemoglobin S concentration, approximately 35% and 70% for Hgb AS and Hgb SS respectively.

The Hgb-S gene is inherited in an autosomal co-dominant pattern. Sickle cell trait has a prevalence of 8 to 14 percent in the African American population and 0.046 percent in Americans not of African descent. It is fairly well accepted that pathological changes are confined to the renal and splenic vascular beds.

There continues to be a significant amount of controversy surrounding sickle cell trait as a risk factor for exercise related morbidity and mortality. Multiple studies performed with treadmills or bicycle ergometery protocols have shown that exercise to exhaustion at sea level regularly induces mild levels (less than 1 %) of reversible sickling in peripheral venous blood.[1-3] The presence of sickled erythrocytes were not associated with physiologic deficits in oxygen transport or consumption, energy metabolism, or pulmonary, cardiac or skeletal muscle function. There was no erythrocyte sickling at rest at sea level. The possibility of volume depletion, dehydration or heat illnesses affecting individuals with sickle cell trait appears to not have been addressed until multiple deaths among military recruits. These were studied retrospectively by many groups with no definitive causal associations found, especially since agonal hypoxemia invariably causes intravascular sickling as an artifact.

Other reported associations such as delayed skeletal maturation, avascular necrosis of bone, complicated migraines, increased fertility, frequency of hospitalization, surgical complications and gallstones, have not been proven to be statistically higher in this population and will not be discussed.

Renal Abnormalities

Hematuria

Hematuria has been fairly well described in multiple studies of individuals with HgbAS.[2-5] However, the difference in susceptibility and frequency of hematuria in sickle cell trait is not well understood. In a study done in Atlanta on 40 patients with sickle cell trait hospitalized during a 14 month period, 7 (18 %) were admitted because of hematuria.[6] A Jamaican study noted unexplained hematuria requiring hospitalization only once in 10 years in 119 patients with sickle cell trait.[3] The causative mechanism of hematuria in sickle cell trait is felt to be the relatively hypertonic, hypoxic and acidotic conditions in the renal medulla, which clearly would be conducive to intravascular sickling. The hematuria is typically painless with at least one report describing a 4:1 increased frequency among males with the trait.[4] Once identified, affected individuals tend to have repeated episodes with no proven association of progression to renal insuffiency or end stage renal disease.

Hyposthenuria

Hyposthenuria, the inability to concentrate the urine, has been well demonstrated in those with sickle cell trait.[8-9] Like hematuria, the mechanism is felt to be sickling in the renal medulla with no gender predilection identified. The initial onset of this concentrating defect is variable but usually occurs early in life. It tends to be intermittent and reversible initially and gradually may become structural and irreversible.[10] Due to this limited capacity to concentrate the urine, there is a decreased ability to compensate for negative water balance during exercise. Hyposthenuria can also be problematic in those individuals undergoing urine drug screening where dilute urine specimens may be perceived as an attempt to conceal illicit drug use.

Splenic Complications

Splenic syndrome in those with HgbAS is described as sequestration or infarction at moderate to high altitude (usually above 10,000 ft). The diagnosis is made primarily by history and physical examination and is characterized by the acute onset of severe left-upper quadrant pain and tenderness along with muscle rigidity. The spleen is usually enlarged and very tender with splinting, left pleural effusion and atelectasis of the left lung. Laboratory findings vary with the degree of sequestration with mild or transient anemia.[11] The etiology is felt to be altitude induced hypoxia typically in unpressurized airplanes but has occurred at mountain altitudes of 5,000 to 7,000 ft above sea level.[12-13] Infarction during high altitude exposure on land usually occurs after heavy physical exertion, which promotes sickling by metabolic effects such as acidosis, hypoxia and dehydration. Several reports[11,14] have observed that the percent of Hgb S in patients with sickle cell trait who had splenic infarction was high, (42 to 44 per cent) compared to the majority of those with the trait who had less than 40 per cent Hgb S, suggesting this as a predisposing factor. Most cases tend to be self-limiting with supportive medical management only. Surgical intervention has seldom been required.

Exertional Heat Illnesses

There has been considerable controversy over the years as to whether sickle cell trait is associated with unexpected death during exercise. The initial reports were centered around the deaths of 39 new military recruits in basic training between 1977 and 1981. In a retrospective and comprehensive review of these deaths, Kark and coworkers[15] demonstrated that the risk of sudden, unexplained death in black recruits with sickle cell trait was approximately 30 times that of black recruits without the trait, and 40 times that

of nonblack recruits. Their analysis revealed that the specific types of death statistically associated with sickle cell trait were exertional rhabdomyolysis, exertional heat illness, and exercise related sudden unexplained cardiac arrhythmia. Exertional heat illness has been somewhat arbitrarily divided into three distinct syndromes; heat exhaustion, heat injury, and heat stroke.[16-17] When muscle necrosis is prominent the syndrome is called exertional rhabdomyolysis[18-19] which may present with or without hyperthermia. The activity most often causing death in the recruits with sickle cell trait was running 1 to 3 miles, (19 of 30 cases) usually at a pace requiring a metabolic rate about 11 to 14 times the basal metabolic rate.[20] The investigators hypothesized that volume depletion or dehydration was the initial pathological event that culminated in an exertional heat illness, or more often rhabdomyolysis. Since 1982 the exercise related mortality of military recruits with sickle cell trait falls close to the background risk for exercise among those with normal Hgb. The reason is felt to be the implementation of regulations by the Army and Navy after the hot summer of 1981 designed to prevent exertional heat illness.

Others have suggested that exertional heat illness is not the initiating cause of unexpected deaths related to sickle cell trait.[21-22] Reference is made of descriptions of several patients with sickle cell trait that died from rhabdomyolysis after relatively light exercise under mild environmental conditions. Also, there have been fewer cases of exercise-related death or life threatening complications reported among civilian athletes with sickle cell trait.

The group advocating the heat illness hypothesis explains the lower mortality among civilian athletes as due to their better overall physical conditioning, ability to readily take breaks from exposure to radiant heat and little use of heat-retaining clothing.

Future Studies

As Africans of various nationalities prosper and career opportunities improve more are flying in airplanes and diving with self contained underwater breathing apparatus (scuba). As previously mentioned, decreasing ambient pressure or partial pressure of oxygen at higher altitudes (usually greater than 10,000 ft) has long been felt to initiate red blood sickling in those with sickle cell trait. The pathophysiology of decompression sickness associated with reduction of barometric pressure at high altitude is felt to be identical to that caused by increasing ambient pressure at depth.[25] Specifically, the formation of nitrogen gas bubbles in the vascular system inciting the cascade of events leading to the bends.

When diving, the nitrogen that is breathed from the scuba equipment passes from the lungs to the blood vessels and subsequently to the tissues, in the process changing from gaseous to dissolved form. As depth increases so does ambient pressure leading to more dissolved nitrogen in tissues. In certain situations, some of which cannot be explained, nitrogen reenters the gas phase before it can be exhaled-leading to the formation of small bubbles. These bubbles which are mostly nitrogen but contain some oxygen and carbon dioxide, are felt to be the "primary pathological event in the pathogenesis of decompression sickness."[26] Outside of the obvious mechanical problems the bubbles present, the body recognizes them as foreign and activates the immune system with platelet and leukocyte aggregation, fibrinolysis, and initiation of the complement and coagulation pathways.[27] Studies have shown an increased hematocrit and decreased platelet count following decompression that is consistent with activation of the thrombin system. Martin and Nichols[28] demonstrated that even in the absence of symptoms of decompression illness, the platelet count decreased as much as sixty eight percent (68%) not during or shortly after the dive, but about 1-2 days later. It took several days to return to pre-dive levels. Increased blood viscosity has been associated with intravascular sickling in both those with HgbAS and HgbSS. On ascent, nitrogen leaves the tissues converting back to gaseous from dissolved form and is exhaled from the lungs. Since

rate of blood flow would alter any tissues ability to uptake or eliminate a dissolved gas, any mechanism associated with slowing intravascular flow would theoretically facilitate decompression sickness.

In view of the physiologic changes known to occur while diving, the question then arises as to whether individuals with sickle cell trait are at increased risk of decompression sickness while diving with scuba equipment. In particular, would these divers be more negatively affected if volume depleted or exercised more vigorously while swimming or diving.

Due to the obvious risk of diving associated sickling in those individuals with sickle cell disease (HgbSS), some physicians have anecdotally extrapolated the contraindications to those with HgbAS.[28] Others have advised that it is safe for patients with HgbAS to dive as long as they have no preexisting anemia and a normal baseline hemoglobin level.[29] There have been no military or civilian studies conducted to determine the effects of diving with scuba equipment in individuals with sickle cell trait.

Summary

Hematuria and hyposthenuria are the two renal pathological processes most often associated with sickle cell trait. Both are self-limiting and are associated with no significant morbidity in this population. Hematuria is still such a relatively rare occurrence such that when it occurs, another etiology should be sought.

It appears prudent to recommend that individuals with sickle cell trait avoid heavy exercise at altitudes of 10,000 feet or higher as hypobaric hypoxemia increases the risk of splenic infarction. Gradual exercise conditioning and acclimatization to the altitude hypoxia would decrease the risk. Individuals with sickle cell trait should avoid situations that may lead to exertional heat illness, which appear to be the major cause of excess mortality. Sufficient hydration should be maintained above levels of intake dictated by thirst, especially before, during and after exercise. Conditioning programs should start slowly and build up gradually from levels easily tolerated to that which is near maximal effort for the individual.

Even though there is a plausible causal relationship, there is no direct evidence that the pathogenesis of these exercise-related deaths involve microvascular obstruction by rigid erythrocytes. The lack of published data on diving in those with HgbAS is probably due to several factors. Relatively few blacks worldwide dive using scuba gear, while the vast majority of divers free-dive for sustenance (conk, lobster, crabs, etc.) usually less than thirty feet. Also, African and Caribbean nations clearly have had more pressing clinical problems to place limited research allocations. As economic conditions improve for blacks in the Diaspora, especially in the U.S. with the worlds largest black middle class, diving with scuba gear for sport and work has increased (unpublished data-National Association of Black Scuba Divers). Clearly, there is a dire need for research into the possible effects of diving with scuba equipment in those with the sickle cell trait.

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