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Sickle Cell Trait from a Metabolic, Renal, and Vascular Perspective: Linking History, Knowledge, and Health

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Abstract Sickle cell trait (SCT) is at the intersection of genetics, social policy, and medicine. SCT occurs in three-hundred million people worldwide and in approximately 8 % of African-Americans. There has been great debate about the influence of SCT on health. Yet data exist, albeit controversial, which suggest that SCT is associated with metabolic derangements that can lead to sudden death after vigorous physical activity, renal dysfunction, thromboembolic events, and stroke. In addition, it has even been postulated that SCT might enhance the vascular complications of diabetes. This review focuses on (a) the scientific breakthroughs that led to the discovery of hemoglobin S, sickle cell disease, and SCT, (b) the history of screening programs in the United States, (c) the incidence and etiology of exercise-related sudden death in military personnel and athletes with SCT, and (d) the data examining the potential chronic disease consequences of SCT from a metabolic, renal, and vascular perspective.

Keywords Sickle cell trait · Newborn screening · Exercise-related sudden death · Exertional sickling · Hematuria · Stroke

Introduction

SCT occurs most frequently in Africa as well as the African Diaspora, central India, and the Arabian Peninsula [1]. Recognized for centuries in malaria-endemic areas of the world, sickle cell disease was first described in 1910 when James Herrick, a physician from Chicago, reported a case of "severe anemia" in a 20-year-old man of West Indian descent [2]. This was followed by three reports, published between 1915 and 1922, which observed that red blood cell sickling occurred within families [3–5]. In 1924, a detailed case series described 10 African-American families with two different forms of the disease: active and latent [6]. In 1926, Cooley and Lee recognized sickle cell disease as the active form and SCT as the latent form [7].

The molecular basis of sickle cell disease was discovered in 1949 when Linus Pauling recognized that the red blood cells of patients with sickle cell disease contained abnormal hemoglobin (hemoglobin S) [8]. Yet with SCT, red blood cells contained nearly equal amounts of normal hemoglobin (hemoglobin A) and hemoglobin S [8]. Also in 1949, Neel and Beet in separate investigations reported that sickle cell disease and SCT are inherited in Mendelian fashion; the former is homozygous and the latter, heterozygous [9, 10]. In 1958, Ingram discovered that a single gene mutation, resulting in substitution of valine for glutamic acid in the β-chain of hemoglobin A, was responsible for the formation of hemoglobin S [11]. Concurrently conducted epidemiological investigations reported that SCT provided protection from malaria [12].

Screening Programs in the United States

The 1972 National Sickle Cell Anemia Control Act allocated major funding for the development of programs to screen for hemoglobin S [13]. The impetus for this 50-fold increase in federal support came from medical advocates who recognized that funding for sickle cell-related conditions was both insufficient and markedly less than for other hereditary diseases [14].

In the year prior to the National Sickle Cell Anemia Control Act, mandatory screening programs were instituted in

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Massachusetts for children defined as "susceptible" to the disease [15]. In 1972, the United States Department of Health, Education, and Welfare recommended screening for sickle cell hemoglobin for all African-American children [15]. By 1973, 34 states had established race-based infant screening programs for sickle hemoglobin [16]. The first race-independent screening program was initiated in New York in 1975 for all infants born in the state [17]. Ten years later, Delaware, Indiana, Maryland, and Texas introduced similar programs [17]. In 1987, the National Institutes of Health, with a goal of 100 % detection, recommended screening for sickle hemoglobin in infants without regard to race [18]. By 1991, there were only 10 states which did not have universal screening of infants for hemoglobin S [17]. However, by 2006, race-independent infant screening programs had been adopted in all 50 states and the District of Columbia [17].

The value of universal screening for the detection of newborn infants with sickle cell disease is to prevent or delay the acute and chronic medical complications of sickle cell disease [19]. In addition, screening also allows for the detection of SCT. However, limited understanding of SCT has led to confusion and widespread propagation of the belief that SCT is a form of disability [13, 15, 20]. In fact, individuals with SCT have faced challenges obtaining health insurance, employment, and enlistment in the armed forces [20–22]. Therefore, misunderstanding and anxiety about SCT is persistent [23, 24]. This review examines the extent and quality of the data on exercise-related sudden death, as well as the association between both venous and arterial disease and SCT. In addition, whether SCT exacerbates the microvascular complications of diabetes is considered.

Exercise-related Sudden Death

The most publicized potential complication of SCT is sudden death in military recruits and student athletes following vigorous physical activity [25–32].

The link between SCT and exercise-related fatal complications initially relied on case reports [4]. To explore further, Kark et al. performed a retrospective review of all deaths in recruits to the United States Armed Forces who entered basic training from 1977 to 1981 [27]. They reported 13 deaths in the initial training period during vigorous physical exercise in African-American recruits with SCT [27]. In an evaluation of Air Force recruits who entered basic training between 1956 and 1996, Drehner et al. identified sudden death during strenuous exercise in five African-Americans with SCT. Four of the five deaths occurred during the summer months [26].

The experience of African-American athletes with SCT mirrors the military experience [29–32]. A review of the Minneapolis Heart Institute Foundation forensic database reported 23 sudden deaths between 1980 and 2010 in African-American junior high, high school, and college athletes with SCT [29]. These deaths occurred early in the training season during vigorous workouts. In each case, collapse and death were preceded by complaints of fatigue, weakness, and muscle cramping consistent with reports of SCT-related deaths in military recruits [25–27, 29].

Etiology

Exercise-related sudden death associated with SCT has been attributed to exertional heat illness as well as rhabdomyolysis, renal failure, and cardiac arrhythmia [33–35]. The pathophysiology of each of these conditions is most likely related to red blood sickling [36]. However, as red blood cell sickling is known to occur postmortem, it is not possible at autopsy to determine the percent of red blood cell sickling which occurred prior to death [27, 36].

Overall, intense exercise induces dehydration, hypoxemia, and metabolic acidosis [34]. In the presence of SCT, these metabolic factors lead in sequence to increased blood viscosity from polymerization of hemoglobin S, red blood cell sickling, increased vascular adhesion by red blood cells, capillary occlusion, and tissue damage [34, 37]. Most importantly, this high blood viscosity during exercise in people with SCT can be reversed by hydration, a finding which factors into policies regarding treatment and prevention [38].

Regulatory Reponses by the United States Military and American Universities

Since 1996, the United States military has not required screening for SCT because universal policies are in place to prevent exercise-induced heat injury during training. The policies include required time for heat acclimation, hydration mandates, and staff education on the early detection and treatment of heat-related illness [39, 40]. In contrast, the National Collegiate Athletic Association (NCAA) does not specify preventive measures, but requires universal screening for SCT for all athletes [40]. The universal screening for SCT in college athletes is controversial. There is fear that mandatory testing will lead to the withholding of athletic scholarships if SCT is detected [39, 40]. Overall, there is little support for the NCAA policy on mandatory testing. The American Society of Hematology, the Sickle Cell Disease Association of America, and the Centers for Disease Control and Prevention support the position of the United States military and recommend universal precautions for all athletes as the best way to protect against heat-induced injury and sudden death [40].

Renal Health

Renal abnormalities associated with SCT are isosthenuria, hematuria, and papillary necrosis [33, 40, 41]. Whether SCT enhances the risk of end-stage renal failure is uncertain [40]. Typically, the renal medulla is a low-oxygen environment. In the setting of SCT, this low oxygen milieu may enhance sickling, capillary occlusion, and micro-infarction [41–43].

Isosthenuria, which is the inability to concentrate the urine, is frequently observed in SCT [33]. In fact, an inverse correlation between urine osmolality and percent of hemoglobin S has been reported [44]. With isosthenuria, it is important to ensure that urinary fluid loss is matched by oral intake.

The association between SCT and hematuria has been described in case studies and evaluated in a retrospective study of 65,154 hospitalized African-American men (7.8 % with SCT) in 13 Veterans Administration Hospitals [33, 41, 42, 45–47]. The prevalence of hematuria was 2.5 % in the men with SCT versus 1.3 % in the men with normal hemoglobin ($P<0.05$) [45]. Therefore, the overall prevalence of hematuria was low in both groups, but nonetheless twice as frequent in the men with SCT.

Papillary necrosis is ischemic damage to the renal medulla and frequently presents with gross hematuria and flank pain [42, 48–50]. In a 1974 prospective study of 200 African-Americans who underwent excretory urography, SCT was identified in 15 and either papillary damage or necrosis was identified in half [50]. Intravenous hydration after papillary necrosis is considered essential [42, 48].

End-Stage Renal Disease

Debate surrounds whether SCT is a risk factor for end-stage renal disease (ESRD) [40, 51, 52]. In support of an association, Derebail et al. reported in 2010 that the prevalence of SCT in 188 African-Americans with ESRD was 15 % [51]. This frequency of SCT was twice as what the census data would have predicted [51]. In contrast, in a 2011 report, Hicks et al. compared the prevalence of SCT in 2081 African-Americans with ESRD and 1171 African-Americans without ESRD. The prevalence of SCT was 7 to 8 %, in both the African-Americans with ESRD and the controls [52]. Both of these studies were well-designed and recent, yet their results are conflicting. Therefore, the effect of SCT on renal function and failure is unresolved.

Vascular Health

Vascular health is specific to circulation and involves either the venous or arterial system. Overall, there is a considerable amount of data examining the association between SCT and venous disease, including deep vein thrombosis and pulmonary embolism. However, limited data exists on the relationship between SCT and the arterial system and is largely confined to case reports. Disorders of the arterial system can be subdivided into large and small vessel disease (macrovascular and microvascular complications). We review the available data on venous and arterial system disorders in the presence of SCT.

Venous System

Two important studies have suggested an association between SCT and venous thromboembolism [45, 53]. The retrospective study of 65,154 hospitalized African-American men (7.8 % with SCT) conducted by Heller et al. identified a significantly higher rate of pulmonary embolism in men with SCT compared to men with normal hemoglobin (2.2 versus 1.5 %, $P<0.001$) [45]. In a cross-sectional study of African-Americans, Austin et al. compared the rates of SCT in 515 patients with either deep vein thrombosis or pulmonary embolism to 555 age- and sex-matched controls [53]. These investigators found that venous thrombosis was two times more common among African-Americans with SCT than African-Americans with normal hemoglobin [53].

Another important area of exploration is whether SCT enhances the underlying risk of venous thromboembolism from hormonal contraceptives. Austin et al. examined the association between SCT and hormonal contraceptives on venous thromboembolism in 60 premenopausal African-American women with venous thromboembolism and 196 age- and race-matched women without venous thromboembolism. The hormonal contraceptives in the 60 women with venous thromboembolism were the oral contraceptive pill in 56 and depot medroxyprogesterone acetate shots in four. Compared to women with no SCT and no hormonal use, the odds ratio of venous thromboembolism in women with only SCT was 1.8 (95 % CI 0.52–6.3). For women with hormonal use but no SCT, the odds ratio of venous thromboembolism was 2.6 (95 % CI 1.1–6.2). In women with both SCT and hormonal use, the odds ratio increased 6 times to 12.1 (95 % CI 2.8–52) [54]. Therefore, the authors conclude that SCT may act synergistically with hormonal contraceptives to enhance the risk of venous thromboembolism [54].

The etiology of thromboembolic events in the presence of SCT has been attributed to hypercoagulability [33, 36]. SCT is known to be associated with increased activity of several coagulation factors, including thrombin-antithrombin complexes, prothrombin fragment 1.2, and d-dimers [55]. Furthermore, data from in vitro experiments has demonstrated that sickled red blood cells enhance clotting [56].

Arterial System

Large Vessel Disease

Most of the data relating SCT to large vessel disease, such as stroke, is found in case reports rather than cross-sectional or prospective studies. In 2005, the Archives of Neurology published three commentaries discussing the relationship between SCT and stroke [57–59]. One author, M.R. Golomb argued in favor of an etiological association between SCT and stroke while the other two authors, E.S. Roach and M.M. Dowling independently argued against it [57–59]. Golomb cites 17 reports of stroke in children and adults with SCT. As no risk factors for stroke were identified, Golumb concluded that SCT had an etiological role in the development of the stroke [58]. To support his argument, Golumb focused on the observation that at autopsy, thrombi of sickled cells were identified in multiple vessels [58].

The commentaries by Roach and Dowling emphasize the lack of evidence for an association between SCT and stroke [57, 59]. Roach argues that independent of SCT, one third of strokes in young adults and children has no obvious cause. Therefore, the presence of the sickle trait by itself is not enough to conclude causality [59]. Dowling emphasized that many patients with both SCT and stroke have confounding factors, such as leukocytosis, hypertension, alcoholism, and history of rheumatic fever [57]. In addition, Dowling cites the ethical and political consequences of SCT-related discrimination that occurred in the 1970s. Until more data is available, he cautioned against attributing stroke to SCT [57].

Therefore, the publication in 2014 of the first prospective analyses of risk of ischemic stroke in African-Americans with and without SCT from the Atherosclerosis Risk in the Community (ARIC) is extremely important [60]. Between 1987 and 2011, 3497 African-Americans with an age range of 45 to 64 years and a prevalence of SCT of 6.4 % were followed. The incidence of ischemic stroke was significantly higher at 13 % in African-Americans with SCT compared to 10 % African-Americans without SCT. Therefore, until more information is available, it is reasonable to be alert to the possibility that SCT represents a risk factor for ischemic stroke.

Small Vessel Disease

Consideration of a Link Between SCT and the Microvascular Complications of Diabetes

As SCT occurs in 8 % of African-Americans and type 2 diabetes occurs in 20 % of African-Americans, it is likely that there are a significant number of African-Americans with both conditions [61, 62]. As microcclusive disease occurs in both sickle cell disease and type 2 diabetes, there has been great speculation that the presence of SCT may exacerbate the small vessel complications of type 2 diabetes such as retinopathy, renal disease, and leg ulcers [63]. Nonetheless, we could only identify four articles which directly address this issue [64–67]. Of the four investigations, only one study which was conducted in Nigeria suggested an association between SCT and the microvascular complications of diabetes in men, but not women [64]. The three other reports conducted in the United States and London revealed that independent of gender, SCT had no impact on the microvascular consequences of diabetes [65–67]. All of the studies are suboptimal in that they were cross-sectional with relatively small sample sizes or SCT was not documented by hemoglobin electrophoresis or genotyping. Nonetheless, the general consensus appears to be that SCT has no effect on the small vessel complications of type 2 diabetes. However, due to the insufficient number of well-designed studies, the effect of SCT on the microvascular complications of diabetes is an important and unresolved issue. In the United States, large prospective studies could be designed or built into existing outcomes studies. The importance of a definitive answer is that it would be valuable to know if there is an increased need for monitoring diabetic complications in the presence of SCT.

Conclusion

Most people with SCT are asymptomatic and unaware of their SCT status. In contrast to sickle cell disease, a homozygous condition with many complications, decades of research seeking to clarify the clinical significance of SCT have provided inconclusive results. Nonetheless, the literature is replete with references to an association between SCT and sudden death during vigorous physical activity as well as vascular and renal abnormalities. Due to insufficient information on the consequences of SCT, the best approach may be universal adherence to best health practices such as avoiding (a) dehydration during strenuous exercise to prevent sudden death, (b) prolonged sitting to lower the risk of venous thrombosis, and (c) remaining alert to the early signs and symptoms of a stroke.

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Consent to submit has been received explicitly from all coauthors. Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

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