Sickle Cell Trait: A Benign State?

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Abstract
Background: Sickle cell trait (SCT) is the heterozygous form of sickle cell disease and expectedly should be a benign state with no complications ascribed to it. There are numerous reports challenging its being a benign condition, though this is controversial. Methods and Results: A review of the results of the accompanying investigations done on some of the patients show that beta thalassemia may be responsible for many of the ascribed symptoms and complications. These patients may therefore have sickle cell beta thalassemia, a compound heterozygous form of sickle cell disease. Conclusion: It is important to screen for beta thalassemia using red cell indices and quantitation of the different hemoglobin fractions before attributing any symptoms to SCT. DNA analysis, though useful in ascertaining the presence of the sickle cell gene, is not sufficient. There is the need to exclude the presence of mutations for beta thalassemia, which often is geographical region-specific.

Key Words
Beta thalassemia trait · Heterozygous state · Misdiagnosis · Silent carrier

Introduction
Sickle cell disease is a heterogeneous group of disorders in which the inheritance of a copy of the sickle cell gene in addition to another abnormal hemoglobin gene results in a disease state. Individuals who are homozygous for the sickle cell gene are mostly affected and manifest a protean of symptoms and complications. Compound heterozygotes such as sickle cell hemoglobin C disease, hemoglobin S/beta thalassemia (Sβthal) have a milder course compared to the homozygous form (HbSS). Expectedly, the heterozygous form HbAS is a benign state since sickle cell anemia (HbSS) is an autosomal recessive disorder. There have been reasons from the scientific literature to doubt if the sickle cell trait (SCT; HbAS) is indeed a benign state. This is because of a high incidence of some pathology found in association with the trait. The earliest publications are of sudden deaths [1, 2] and were noticed in athletes [3, 4]. However, other complications such as renal disorders [5], veno-occlusive disease [6] and diabetes mellitus [7] have lately been ascribed to it despite which the life expectancy of a person with this trait is not reduced [8]. If indeed these complications are associated with SCT, then SCT is not a benign state; HbA and HbS are therefore co-dominant, making HbAS a compound
heterozygote state. The objective of this paper is to probe into the likelihood of SCT being a benign state through a scientific literature review.

Epidemiology

The prevalence of SCT is highest in Africans and is seen mostly in African descent in other parts of the world. Nigeria probably has the highest number of people with the trait, not just because of its high population but also because of a high prevalence of 25–30% [9]. The distributions in other parts of Africa are between 10–15% for Liberia, Ghana and Uganda [10–12], respectively, Cameroon and the Republic of Gabon, a central African country, have a prevalence of 19 and 22%, respectively, closer to the prevalence in Nigeria than to other African countries [13, 14]. Review of data from two decades of newborn screening in the United States revealed a prevalence of 1.5% [15], but the prevalence in African Americans is about 8% [16], which is similar to that of other African populations who migrated out of Africa as a result of the slave trade. As in African Americans, the prevalence in Brazil and Jamaica is about 10% [17, 18]. The rising prevalence of the traits in other western populations is now of concern and public health significance. Recently, a survey through newborn screening among German immigrants showed a prevalence of 22 per 1,000 births [19]. It is estimated that about 1% of the European population now carry a gene for hemoglobinopathy, the majority of which codes for the sickle cell gene [8]. The global distribution of SCT therefore calls for a need to ascertain if the pathologies attributed to it are indeed factual.

Protective Effect of SCT

SCT is one of the red-cell polymorphisms known to protect against severe forms of malaria in tropical Africa. The protection conferred by SCT on malaria is believed to be responsible for the sustenance of the disorders in this region of the world. Although the association between SCT and Plasmodium falciparum, a causative agent for malaria, is known, the strength of this association and its full ramification is yet to be uncovered [14]. There is now evidence that individuals who inherit the SCT along with alpha thalassemia trait experience much lower protection from malaria than those with SCT alone [20]. Another genetic disorder that is also protective against Plasmodium falciparum infection is glucose-6-phosphate dehydrogenase [21], but the effect of the co-inheritance of G6PD and SCT is yet to be explored. Recently too, the protective effect of SCT on endemic Burkitt’s lymphoma has been challenged since the frequencies of SCT does not differ between children with Burkitt’s lymphoma and healthy children [22].

Renal Complications

The percentage concentration of HbS affects renal function, and co-inheritance of alpha thalassemia is related to the ability of affected persons to concentrate urine. Deletion of one or two chains in an individual with SCT is associated with a better concentrating ability of the kidney [23] since this reduces the percentage concentration of HbS. Micro infarcts occurring in the renal medulla as a result of extreme hypoxia, acidosis or hypertonicity may be responsible for the inability to concentrate urine, while the corresponding papillary necrosis may result in microscopic hematuria [23] and sometimes in gross hematuria. It has been suggested that SCT may not be responsible for the observed papillary necrosis and hematuria since it could also occur in people without the trait [23]. Among patients with end-stage renal disease (ESRD), the prevalence of SCT was found to be higher in studies done in African Americans, thus making SCT a possible risk factor for ESRD [8, 24]. Contrary to this, a study of Congolese individuals reported no difference in the frequency of SCT in patients with ESRD compared to the general population [25], typifying the controversy on SCT as a risk factor for ESRD. Despite this, the odds for a higher dose of erythropoietin in ESRD in patients with hemoglobin variants (mostly SCT) are twice that of those with a normal phenotype [26]. An important implication of SCT as a risk factor for ESRD is a decision on whether to use these individuals as donors for kidney transplant. Renal medullary carcinoma is also more prevalent than renal cell carcinoma in SCT patients when compared with non-SCT individuals [8, 23].

Incident Stroke

Case reports of SCT as an independent risk factor for stroke prompted a prospective study to determine its role in stroke. It was observed that incident stroke is more frequent among SCT subjects compared to their homozygous HbA counterparts [27] after adjusting for other risk factors for stroke. The adjusted covariates include hyper-

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tension and diabetes mellitus. The adjustment for these covariates might have reduced the effect of the observed association since hypertension is likely to be an intermediate factor in the progression to chronic kidney disease by SCT. There are also reports linking diabetes and SCT.

**Thromboembolic Disorders**

Individuals with SCT are now known to carry a similar risk to venous thromboembolism (VTE) as sickle cell disease patients. This is highlighted by a case-control study, which showed a 2-fold and 4-fold increase in VTE and pulmonary embolism (PE), respectively [28], and two hospital-based studies that reported approximately a 40% increased risk of PE [29, 30] in SCT individuals compared to subjects without the trait. These findings were confirmed by a cohort multicenter study, which showed that though SCT (confirmed the presence of SCT by DNA analysis) increases the risk of PE by two fold it does not increase the risk of deep venous thrombosis [31]. All studies were conducted in African Americans. However, SCT was not found to be associated with an increased VTE risk in pregnancy and postpartum in black women. Data were obtained over an 11-year period from the women’s first delivery record. Ascertainment of SCT was done by high performance liquid chromatography to determine the percentage of the different hemoglobin fractions, thereby excluding women with beta thalassemia trait (BTT), i.e. elevated HbA2 >3.5% and fetal hemoglobin (Hbf) >1% [32]. Other thromboembolic disorders include a case of central retinal occlusion in an Arab teenager with SCT and an abnormal partial thromboplastin time [33] and splanchnic venous thrombosis in a 24-year-old Indian with negative prothrombotic markers for thrombophilia [6].

**Type 2 Diabetes Mellitus**

A study in Africans revealed that male diabetics with SCT have a higher risk for complications compared to those with normal hemoglobin, with the patients having a greater proportion of proteinuria or retinopathy than those with normal hemoglobin [34]. This is in contrast to another study among Africans, which did not find any association between type 2 diabetes mellitus (T2D) and SCT. The study observed that the prevalence of 19% for SCT among the patients is comparable with the prevalence in the general population [13]. Another study in African Americans concluded that SCT does not increase the risk of microvascular complications. After adjusting for T2D and other factors, the observed higher prevalence in retinopathy, peripheral vascular disease and ESRD in non-SCT diabetics compared to SCT diabetics no longer existed [35]. This study may be interpreted as showing that T2D is a positive confounder in the association between SCT and the analyzed complications. In addition, the data showed a higher prevalence of 29% compared to the prevalence of 8% in the African American population [16]. Though sickle cell retinopathy was also reported in a patient with gestational diabetes and hypertension [36], this was contradicted by a study concluding that there is no association between SCT and diabetic retinopathy after comparing diabetic patients with and without retinopathy. This again is despite the fact that 3 of the 4 SCT patients developed new vessels within 3 years of diagnosis of diabetes compared to 4 of 23 patients with normal hemoglobin [37].

**Sickle Cell Retinopathy**

Proliferative sickle cell retinopathy is commonly associated with sickle cell beta thalassemia or sickle cell disease [36], but there are reports of such in individuals with the SCT. A significant positive correlation was found between the severity of conjunctival vasculopathy and the percentage of sickle hemoglobin in 65 subjects with various sickle cell hemoglobinopathies, which included SCT [38]. In a report of 3 cases with sickle cell retinopathy, 1 was associated with traumatic hyphema and raised intraocular pressure, while the other 2 were associated with diabetes [39], leading to the conclusion that the sickle cell retinopathy is related more to the associated systemic pathologies. To assess if sickle cell retinopathy was as a result of accompanying systemic pathologies or not ophthalmic examination was performed on parents of children with sickle cell anemia. After confirming the HbAS status of the parents, no evidence of sickle cell retinopathy was seen in the 32 individuals who agreed to be part of the study. Though the response rate was poor (32%) [40], this led to the conclusion that sickle cell retinopathy is unassociated with SCT.

**Preeclampsia**

Preeclampsia was found to be significantly higher in African American women with SCT than in SCT-negative women. Similarly, SCT women are more likely to re-
port preeclampsia in a previous pregnancy; they also have a significantly reduced gestational age at delivery and therefore low birth weights. There was, however, no significant difference in the rate of chronic hypertension or diabetes in both groups [41]. This association of preeclampsia with SCT was not observed in a retrospective cohort study, which rather noted that the SCT cohorts are more likely to have gestational diabetes and a higher mean body mass index [42].

Diagnosis

These various reports have highlighted the controversies in the relationship between SCT and the associated complications. Though some of these are isolated case reports, others are observational studies, which may therefore not be free of confounding factors and other challenges of observational studies. Case ascertainment may also be an underlying problem responsible for these controversies. A closer look at some of the case reports show that some of them could have been cases of Sβthal. Apart from DNA analysis, which is confirmatory, an elevated level of HbA₂ (>3.5%) is the hallmark of BTT, though normal levels of HbA₂ could occur in silent carriers of the trait [43]. Furthermore, when HbS is inherited along with beta thalassemia, the percentage concentration of HbS is >50% in Sβthal, while it is <50% in HbAS. In addition to this, low red cell indices, a mean corpuscular hemoglobin (MCH) level of <27 pg and/or a mean corpuscular volume (MCV) of <80 fl are useful in screening for alpha or beta thalassemia. The results of the laboratory investigations of some of the case reports are suggestive of Sβthal. The 24-year-old male with splanchnic venous thrombosis [6] had low red cell indices with borderline HbA₂ (MCH 76.7 fl, MCH 24.7 pg, HbA₂ 3.3%, HbS 35.8%, HbA 54.5%, HbF 0.8%). The patient with central retinal artery occlusion was a 14-year-old Arab Asian [32] with the following parameters (HbA₂ 3.86%, HbA 58% and HbS 38.23%), while the results of the 29-year-old black woman with proliferative sickle cell retinopathy and gestational diabetes [36] showed HbA₂ 5.0%, HbS 35% and HbA 53%. Though none of the cases had the required HbS concentration of >50% expected in Sβthal, it should also be noted that they also had HbA levels below 60%. In 2 of the cases [6, 36], the total of the hemoglobin fractions falls short of the expected 100%, while in the third patient, the total is slightly above 100%, which may suggest the presence of other hemoglobin fractions, rounding errors or inaccurate quantitation. The method used for hemoglobin electrophoresis was stated only in 1 case [6] and it was by high performance liquid chromatography, which may be the reason why the level of HbF was also recorded. The method for analyses or the HbF value was not stated in the 2 other cases. The level of HbF in the patient [6] is normal (<1%), while about a third of the patients with BTT will have elevated HbF levels [43]. A case-control study of SCT individuals with symptoms suggestive of hemoglobinopathy showed that BTT is likely to be responsible for the observed symptoms [44]. It is therefore important to exclude BTT before ascribing disease states or complications to SCT.

Conclusion

Though there are reports from the scientific literature challenging SCT as a benign state, there are other reports doing the contrary. Most reports are from observational studies, which may not be free of confounding factors. At the background of the controversy is the possibility that some of the cases may indeed be patients with Sβthal who have been misdiagnosed as SCT. It is therefore important to rule out the likelihood of BTT before ascribing any symptoms to the SCT. This could be done first by screening, using red cell indices, and then by quantifying the various hemoglobin fractions. It should, however, be noted that screening alone may miss some silent carriers of BTT. DNA analysis to ascertain the presence of the sickle cell gene may not be sufficient in the presence of mutations of beta thalassemia. Exclusion of beta thalassemia will require knowledge of the racial background since mutations for beta thalassemia are a myriad and often region-specific.

Disclosure Statement

The author declares no conflict of interest.

References


