A Review of Clinical Profile in Sickle Cell Traits

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Abstract

Sickle cell trait is not usually regarded as a disease state because it has complications that are either uncommon or mild. Nevertheless, under unusual circumstances, serious morbidity or mortality can result from complications related to polymerization of deoxy-hemoglobin S. A previous study was earlier conducted to study Sickle cell traits and it revealed that there was enhanced lipid per oxidation along with imbalance in the pro-oxidant and antioxidant status in patients with sickle cell anaemia. Moreover, sickle cell traits present with varied problems including increased urinary tract infection in women, gross hematuria, complications of hyphema, splenic infarction with altitude hypoxia or exercise, life-threatening complications of exercise etc. Renal medullary carcinoma in the young, early onset of end stage renal, as well as disease from autosomal dominant polycystic kidney disease are other well known occurrences in sickle cell traits. In view of the above facts, this article aims to review the literature to analyze the health status in sickle cell traits.

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Sickle cell disease refers to a collection of genetic blood disorders characterized by a hemoglobin variant called HbS. Individuals who are affected with sickle cell anemia have two copies of this beta globin variant, and the primary hemoglobin present in their red blood cells is HbS. This disease is particularly common among people whose ancestors come from sub-Saharan Africa, Spanish-speaking regions (South America, Cuba, Central America), Saudi Arabia, Oman, India, and Mediterranean countries such as Turkey, Greece, and Italy.

In an earlier study, the pro-oxidants and anti-oxidant status in patients with sickle cell anaemia were assessed. Although available reports suggested that sickle cell erythrocytes are susceptible to endogenous free radical mediated oxidant damage, there remains some discrepancy in the status of antioxidant enzymes and antioxidant vitamins in these patients. In view of this, 107 cases of sickle cell anaemia (36 'SS' and 71 'AS' pattern - as confirmed by haemoglobin electrophoresis) were subjected to analysis of malondialdehyde, ascorbic acid, superoxide dismutase and albumin. The results were compared with 54 healthy controls (age and sex matched). The results indicated a marked increase in lipid peroxidation and superoxide dismutase levels in both 'SS' and 'AS' types of sickle cell anaemia compared to controls. Although no difference was observed in the levels of albumin in both groups, the levels of ascorbic acid were significantly depleted in sickle cell anaemic patients. The results are indicative of enhanced lipid per oxidation along with imbalance in the pro-oxidant and antioxidant status in patients with sickle cell anaemia.[1] (Table 1)

Table 1: Levels of Malondialdehyde, Superoxide Dismutase, Vitamin C, Haemoglobin and Albumin in Total Cases and Control

Parameters	HbSS	HbAS	Controls
MDA (m mol/L)	*4.15 (0.30 ±)	*2.52 (0.33 ±)	1.83 (0.22 ±)
SOD (U/ml)	*323.83 (20.04 ±)	*255.87 (27.66 ±)	199.14 (21.11 ±)
SOD (U/gHb)	*4989.48 (159.50 ±)	*2123.77 (334.63 ±)	1391.87 (58.34 ±)
Vitamin C (mg %)	0.44# (0.04 ±)	0.64# (0.04 ±)	0.93 (0.08 ±)
Haemoglobin (gm %)	6.5# (0.44 ±)	12.31# (1.56 ±)	14.22 (1.10 ±)
Albumin (gm %)	** 4.05 (0.33 ±)	**3.99 (0.35 ±)	4.09 (0.46 ±)

*Significantly higher ($p<0.001$) as compare to controls, **Not significantly different from controls, # Significantly lower ($p<0.001$) as compared to controls.

In this study, the role of serum uric acid as an anti-oxidant in sickle cell anaemia was evaluated and the results showed that enhanced oxidative stress in sickle cell anaemia was counteracted by antioxidant uric acid leading to lower uric acid levels.[2]

These facts gave an impetus to have a detailed clinical review of the health profile in patients with sickle cell disease.

Table 2: Levels of MDA and Endogenous Anti-oxidants in Patients and Control.

Parameters	Control (n=48)	SCA cases (n=60)
Plasma MDA (μmol/L)	1.83 ± 0.22	4.17 ± 0.28*
Serum Uric acid (mg %)	4.2 ± 0.74	2.93 ± 0.74 *#
Serum total bilirubin (mg %)	0.48 ± 0.17	1.74 ± 0.51
Serum albumin (gm %)	3.63 ± 0.29	3.7 ± 0.33

* Significantly different as compared to controls; $p<0.001$
\# Significantly negative correlation (r = 0.86): $p<0.001$

Sickle cell anemia is an inherited autosomal recessive disorder characterized primarily by chronic anemia and periodic episodes of pain.[3] Individuals who possess one copy of the normal beta globin gene (HbA) and one copy of the sickle variant (HbS) are referred to as having the sickle cell trait, but these individuals do not express symptoms of sickle cell disease. Hence, sickle cell traits present with varied problems including increased urinary tract infection in women, gross hematuria, complications of hyphema, splenic infarction with altitude hypoxia or exercise, and life-threatening complications of exercise, exertional heat illness (exertional rhabdomyolysis, heat stroke, or renal failure) or idiopathic sudden death.[3,4,5,6]

Complications and Risks Associated with Sickle Cell Trait[5,6]
1. Splenic infarction at high altitude, with exercise, or with hypoxemia
2. Isothenuria with loss of maximal renal concentrating abilitty
3. Hematuria secondary to renal papillary necrosis
4. Fatal exertional heat illness with exercise
5. Sudden idiopathic death with exercise
6. Glaucoma or recurrent hyphema following a first episode of hyphema
7. Bacteruria in women
8. Bacteruria or pyelonephritis associated with pregnancy
9. Renal medullary carcinoma in young people (ages 11 to 39 years)
10. Early onset of end stage renal disease from autosomal dominant polycystic kidney.

Hematological Manifestations
Pathologic processes that cause hypoxia, acidosis, dehydration, hyperosmolality, hypothermia, or elevated erythrocyte 2, 3-DPG can transform silent sickle cell trait into a syndrome resembling sickle cell disease with vaso-occlusion due to rigid erythrocytes.

Compound heterozygous sickle cell disease can be mistaken as uncomplicated sickle cell trait, particularly when an unusual globin variant is involved.

People with uncomplicated sickle cell trait have a normal blood examination as assessed by conventional clinical methods, including normal red cell morphology, indices, reticulocyte counts, and red blood cell survival by chromium labeling. Conventional methods of detecting hemolysis are negative, such as measurements of serum haptoglobin, bilirubin, and LDH. Erythrocyte density distribution is normal, adherence to endothelium is not increased, altered membrane lipids and proteins are not detectable, cytoplasmic inside-out vesicles with high calcium content are absent, and permanently distorted erythrocytes are not observed.

Life - Threatening Complications of Exercise
An important potential complication of sickle cell trait is unexpected exercise-related death (ERD). The validity of this association aroused heated controversy.[4] The possibility that previously healthy young people with sickle cell trait might suffer increased mortality from exercise was first suggested by observations of enlisted recruits in US Armed Forces basic training. A military trainee with Hb AS suffered exercise related hypernatremia during physical training in the field. He only survived a critical illness that included acute renal failure because of dialysis.[7,8,9,10] During a single summer, there were four exercise-related deaths among recruits at Fort Bliss, all of whom were black and had sickle cell trait, while no recruits with normal hemoglobin died. Only 1.5% of these recruits had sickle cell trait. The authors suggested a significant risk association with sickle cell trait.[10]

The recommendations for safe exercise by individuals with sickle cell trait are based upon the premise that the predominant cause of excess morbidity and mortality is preventable exertional heat illness. At least half of these cases were proven to suffer from acute exertional heat illness, with rhabdomyolysis as the predominant component. The other half of cases died suddenly without a clear etiology, but with evidence for increased risk of unrecognized EHI when such evidence was sought. The controlled study supporting this view has not undergone peer review and publication.

Splenic Infarction from sickle cell trait is more common with exercise at high altitude but has occurred with altitude exposure at rest or with exercise at sea level.[5] The spleen is unusually susceptible to vaso-occlusion related to hemoglobin S polymerization and red cell deformation. When persons with hemoglobin S are exposed acutely to high altitude hypoxia, the spleen is the organ most consistently injured by micro-vascular obstruction. Splenic infarction usually presents as severe abdominal pain localizing

within a few hours to the left upper quadrant, accompanied by nausea and vomiting. Splinting of the left hemithorax, left pleural effusion, and atelectasis of the left lung often follow.

A tender enlarged spleen often becomes palpable. Fever, leukocytosis, and an acute elevation of serum LDH (Lactate dehydrogenase) level occur during the first 72 hours out of proportion to serum CK (creatinine kinase) levels. Splenic infarcts are best imaged by CT scan, which usually shows a few large regions of hemorrhage of variable size. Often small hemorrhages collect outside the splenic capsule.[9,10]

Renal Complications

Examination of maximal urinary concentrating ability in people with sickle cell trait relative to alpha globin gene number demonstrated that one or two alpha globin gene deletions were associated with better preserved renal function.[7]

In other words, the less hemoglobin S that was present, the less renal function that was lost. This implied a significant role of polymerized hemoglobin S in the pathogenesis of renal isosthenuria. In some instances, the anatomic lesions due to sickle cell trait are so distinct that a relationship to polymerization of Hb S can be reasonably inferred. Such complications of sickle cell trait include glaucoma or recurrence after treatment for hyphema and splenic infarction in the absence of primary trauma, infection, inflammation or tumor in the spleen.[9,11,12]

People with sickle cell trait often experience subclinical tissue infarction from microvascular obstruction by rigid erythrocytes. Most people with sickle cell trait develop microscopic infarction of the renal medulla because of extreme hypoxemia, hypertonicity, acidosis, and hyperthermia of arterial blood passing through the long vasa recta of the renal medulla promote polymerization of deoxy-hemoglobin S.[8]

Flow through these vessels requires more than ten seconds, providing an unusually long exposure time for polymerization of hemoglobin S. Cumulative focal lesions result in loss of maximal urine concentrating ability which is progressive with age and develops in most adults with sickle cell trait.[7,8] The functional defect limits urine concentration to approximately the osmolality of serum, causing isosthenuria rather than hyposthenuria. In people with sickle cell trait, urine osmolality can usually reach values higher than plasma during overnight dehydration (400 to 800 mOsmol). Although one may speculate that this lesion might predispose to the development of mild exertional heat illness (EHI) during exercise in hot weather, clinically significant problems related to this deficit have not been demonstrated. Necrosis of the renal papillae can result in hematuria, which is usually microscopic. Gross hematuria is occasionally provoked by heavy exercise or occurs spontaneously.[5,10]

Hematuria

The frequency of hematuria with sickle cell trait from renal papillary necrosis has been accurately measured in a single large study of elderly patients in Veterans Hospitals.[9] Patients with sickle cell trait had a 4% admission rate for hematuria, a significantly higher rate than the 2% admission rate for patients with normal hemoglobin. The absolute rate of substantial hematuria requiring admission was probably higher than would be the case for a population not selected by hospitalization.

It is reasonable to conclude that sickle cell trait results in an approximate doubling of the incidence of hematuria from an unknown absolute incidence of 2% or less of hospitalizations. This implies that hematuria in people with sickle cell trait is often unrelated to sickling or papillary necrosis.[8,9]

Urinary Tract Infection

Studies in Jamaica, England and America established that the rates of urinary tract infection are higher for women with sickle cell trait in comparison to racially matched controls.[3,4,6,8] This is best established for asymptomatic bacteruria of pregnancy, in which the rate is approximately doubled with sickle cell trait.[12] Rates of pyelonephritis may be modestly increased during pregnancy.

Autosomal Dominant Polycystic Kidney Disease

Studies of families with autosomal dominant polycystic kidney disease indicate that the incidence of end stage renal failure from this disorder is identical for Caucaseans and Afro-Caribbeans, but that the age of onset of end stage renal failure is lower for Afro-Caribbean people with sickle cell trait (38 years versus 48 years, $p<0.003$). Half of 12 Afro-Caribbean patients on dialysis for this disorder had sickle cell trait, as opposed to 7.5% of 80 Afro-Caribbean patients on renal dialysis for other conditions. Sickle cell trait is an important risk factor for early onset of renal failure in patients with autosomal dominant polycystic kidney disease.[13]

Renal Medullary Carcinoma

Over a period of 22 years, the Genitourinary Pathology Department of the Armed Forces Institute of Pathology collected 34 cases of a unique neoplasm, which they named renal medullary carcinoma.[14] This is a highly aggressive carcinoma with unique radiologic signs and anatomic and microscopic histology. Thirty-three of the thirty-four cases they described had hemoglobin S (32 with Hb AS and one with Hb SC) and all the known victims were young people aged 11 to 39. When race was known all were Afro-Caribbeans. Males predominated by 3:1 to age 24, after which the case number was similar by gender.

This very rare carcinoma has unusual biologic features since it was largely restricted to patients of African ancestry who were between 11 and 39 years of age. The relative rates of presentation with sickle cell trait versus sickle cell disease are approximately the same as the prevalence of these two genotypes (40 to one). In contrast to this, the prevalence of renal cell carcinoma, a much more common tumor in this age group, is nearly 17 times higher than predicted in people with sickle cell disease but not higher than in people with sickle cell trait.[15,16] Early diagnosis of renal medullary carcinoma at a time which would improve survival has not yet been possible.

Other Medical Complications Associated with Sickle Cell Traits
Pulmonary

In a large study of hospitalized veterans at a median age of 49 years, Heller et al. found a statistically significant association between surrogate markers for pulmonary embolism and sickle cell trait.[11]

Among patients with sickle cell trait diagnosed with pulmonary embolism the frequency of thrombophlebitis was significantly higher but the frequency of hemoptysis was significantly lower. This study demonstrated a two-fold increase in essential hematuria.

A study of 355 hospitalized Afro-Caribbeans men with sickle cell trait was conducted to examine stratification of risk by hemoglobin S fraction for pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, and idiopathic hematuria. Hemoglobin S did not influence the frequency of these syndromes, providing evidence that sickling is not associated with these forms of vascular disease. However, the absence of a significant difference for hematuria, which was influenced by hemoglobin S concentration in a larger study, suggests that this study was not sufficiently sensitive.[11,13]

Complications during Surgery

Isolated case reports of unusual adverse events raise the possibility that surgery involving hypoxia or reduced perfusion could result in vaso-occlusion and serious complications for people with sickle cell trait. Some have recommended exchange transfusion to reduce the fraction of cells containing hemoglobin S prior to the tourniquet surgery or for intra-thoracic surgery, especially open-heart surgery on cardio-pulmonary bypass.[17] However, the best published controlled study appeared to show no additional risk for people with sickle cell trait who were not transfused, including some intra-thoracic cases.[18] A subsequent controlled study of open heart surgery in Africa was interpreted as showing no adverse effects related to sickling for 11 patients with sickle cell trait and two with doubly heterozygous sickle cell disease.[19] However, two patients with sickle cell trait died from complications of surgery.

The authors attributed these deaths to unavoidable risk from severe cardiac lesions rather than any effect from sickling.

Occular Complications

People with sickle cell trait are more susceptible to complications following treatment of hyphema. Slow flow of relatively hypoxic fluid in the chamber of the eye out of the filtration apparatus is a location in which both polymerization of hemoglobin S and obstruction of flow by rigid erythrocytes is likely.[3,4,6] This can result in glaucoma and secondary hemorrhage. In a study from Tennessee of 99 eyes from 97 children with hyphema, secondary hemorrhage only occurred in 14 eyes of 13 children with sickle cell trait. The frequency with sickle cell trait was 64%, significantly higher than among 57 eyes without sickle cell trait (0%).

Complications attributed by some to sickle cell trait include proliferative retinopathy, worsening of diabetic retinopathy, stroke, myocardial infarction, leg ulcers, avascular necrosis and arthritis of joints, and increased frequency of the bends from diving. There is no convincing evidence that sickle cell trait increases the incidence of these problems.

Some case reports may represent situations in which other variants of beta or alpha globin produced undiagnosed sickle cell disease.[4,6,20,21] Others may be the consequence of phenotypes with increased 2,3-DPG or with arterial desaturation which has increased the rate of polymerization of hemoglobin S sufficiently to convert a patient with sickle cell trait into phenotypic sickle cell disease.[6,18,22]

A Variant Expression of Hemoglobin S Antilles

In 1986, Jean Rosa et al. in Paris evaluated a patient who had symptoms consistent with sickle cell disease, including recurrent episodes of pain crisis. The patient's hemoglobin evaluation by electrophoresis and HPLC showed evidence only of sickle trait. Structural analysis of the patient's hemoglobin S gene revealed two mutations. The expected mutation of glutamic acid to valine at position ß-6 was accompanied by a second substitution at position ß-23 of valine to isoleucine.[23,24] Since the mutation at ß-23 produced no chance in the charge of the hemoglobin, it separated identically to hemoglobin S by standard techniques.

Only analysis at the level of a research laboratory can detect the second abnormality in the hemoglobin molecule. The mutant hemoglobin was named hemoglobin S Antilles, since the patient came to Paris from the French Antilles. Hemoglobin S Antilles is much less soluble than hemoglobin S. The consequence is that people heterozygous for hemoglobin A and hemoglobin S Antilles

have symptoms and complications similar to those of patients with homozygous sickle cell disease.[24,25]

Conclusion

People with sickle cell disease can live full lives and enjoy most of the activities that other people do. There are things that people with sickle cell disease can do to stay as healthy as possible.[25,26,27] Below are a few examples:

- *Get regular checkups.* Regular health checkups with a primary care doctor can help prevent some serious problems.
- *Prevent infections.* Common illnesses, like the flu, can quickly become dangerous for a child with sickle cell disease. The best defense is to take simple steps to help prevent infections.
- *Learn healthy habits.* People with sickle cell disease should drink 8 to 10 glasses of water every day and eat healthy food. They also should try not to get too hot, too cold, or too tired.
- *Look for clinical studies.* New clinical research studies are happening all the time to find better treatments and, hopefully, a cure for sickle cell disease. People who participate in these studies might have access to new medicines and treatment options.
- *Get support.* Find a patient support group or community-based organization in your area that can provide information, assistance, and support.

Although there has been extensive clinical and basic science research in SCD, many public health issues, such as blood safety surveillance, compliance with immunizations, follow-up of newborns with positive screening tests, stroke prevention, pregnancy complications, pain prevention, quality of life, and thrombosis, in people with SCT remain unaddressed. Currently, efforts are under way to strengthen SCD-related activities within the Center for Disease Control and Prevention (CDC).[27] In the US, all states and the District of Columbia have universal newborn screening (NBS) programs for sickle cell disease (SCD), which also identify sickle cell trait.

Local screening activities may have had an impact on participation in specialized SCD care and the disease-associated mortality rate. The incidence of Hb SS has remained unchanged over 27 years, and that of Hb S trait and the S allele has been unaffected in the last 18 years. Trait notification goals and approaches should be reevaluated. There is significant misinformation about what it means to be a carrier and its health and reproductive implications. Formal professional counseling is rare, especially for those families without an affected proband. Strategies to increase the utilization of counseling and improve genetic literacy are necessary.[26,28,29]

Acknowledgements

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