The Splenic Syndrome in Individuals with Sick Cell Trait

Jessica Goodman,¹ Kathryn Hassell,² David Irwin,³ Ewa H. Witkowski,⁴ and Rachelle Nuss^{2,5}

Abstract

Goodman, Jessica, Kathryn Hassell, David Irwin, Ewa H. Witkowski, and Rachelle Nuss. The splenic syndrome in individuals with sickle cell trait. *High Alt Med Biol* 15:468–471, 2014.—The medical records of 25 individuals with sickle cell trait and altitude-associated splenic infarct, reported to two Colorado physicians, were reviewed. Electrospray mass spectroscopy was performed on blood samples from a cohort of 10 of the individuals to rapidly confirm beta hemoglobin phenotype. Only males were identified with a 1.4:1 ratio of non-African Americans to African Americans, and 44% of African Americans and 85% of non-African Americans were unaware they had sickle cell trait. Left upper quadrant pain and an elevated bilirubin were nearly uniformly present. Either abdominal CT or ultrasound was confirmatory. Conservative treatment at a lower altitude generally resulted in a favorable outcome.

Key Words: altitude; sickle cell; sickle cell trait; splenic infarction; splenic syndrome

Introduction

SICKLE CELL TRAIT AFFECTS approximately three million people in the United States, including eight percent of African Americans but also individuals from a variety of other ethnicities, albeit at a lower prevalence. Individuals with sickle cell trait generally live normal lives.

Unlike sickle cell disease, a serious illness in which patients have two sickle (S) genes that cause the production of abnormal hemoglobin, individuals with sickle cell trait carry a defective S gene and a normal A gene. Individuals with sickle cell trait have normal hemoglobin and red cell levels in contrast to those with sickle cell disease. The diagnosis of sickle cell trait is commonly made by hemoglobin electrophoresis or high performance liquid chromatography. Normal A hemoglobin is present at 50%–60% and sickle 35%–45% of the total hemoglobin; however ranges vary depending on the laboratory technique and whether an individual has alpha thalassemia.

Splenic syndrome, a serious health hazard, is precipitated by ascent to moderate to high altitude (Lane and Githens, 1985). Since Colorado has the highest mean altitude (6800 ft) among the 50 U.S. states, has a population of over five million (70% White not Hispanic; 21% Hispanic; and 4.3% African American), and has 57 million visitors each year, it is likely the U.S. epicenter of the splenic syndrome.

It is important that clinicians in Colorado recognize the splenic syndrome and clinicians outside of Colorado, whose sickle cell trait positive patients travel to Colorado for strenuous outdoor activities, counsel their patients about their risk for splenic syndrome.

Universal newborn screening for sickle cell trait in the United States since 2008 makes counseling possible. Herein we report on our observations of the splenic syndrome over a 20-year period and discuss the presumptive associated pathophysiology.

Methods

All individuals who presented or were reported to the Colorado pediatric and adult sickle cell physicians from 1986–2006 with the splenic syndrome, comprise the series. Written, informed consent was obtained by the treating physician from the first ten affected individuals, with approval of the Colorado Multiple Institution Review Board, for medical record access and prospective hemoglobin analysis. Subsequently, the investigators sought an exemption from consent for retrospective medical record review, which was granted by the Colorado Multiple Institutional Review Board for the subsequent 15 individuals who presented to mountain resort clinics and/or Denver-area hospitals with splenic infarction and a history of sickle cell trait or

¹St. Vincent's Children's Hospital, Indianapolis, Indiana.

²Colorado Sickle Cell Treatment and Research Center, ³Cardiology at the University of Colorado, and ⁵The Children's Hospital, Aurora, Colorado.

⁴Department of Cell and Tissue Biology at the University of California San Francisco, San Francisco, California.

who were subsequently diagnosed with sickle cell trait and whose physicians contacted one of the two authors (RN and KH). Laboratory testing was thus limited to that performed as part of clinical care for these 15 individuals.

For the cohort of ten who were prospectively studied, cellulose acetate hemoglobin electrophoresis, with citrate agar confirmation, or isoelectric focusing was performed in the University of Colorado Clinical Laboratory. Blood samples from the cohort were also sent to the Children's Hospital Oakland Research Institute for electro spray ionization mass spectrometry (ESI MS) and reversed phase high performance liquid chromatography (RP HPLC) analyses, which were performed using previously described techniques to confirm beta hemoglobin phenotype (Lubing et al., 1991, Shackelton et al., 1991, Lane et al., 1993; Shackelton and Witkowska, 1996).

Clinical and laboratory data were retrospectively collected from the medical records of all the affected individuals. The variables analyzed from medical records included: age at event, gender, ethnicity, knowledge of having sickle cell trait, home residence, highest altitude exposure, signs, symptoms, laboratory findings, diagnostic imaging, treatment, and outcome. Results of conventional solubility testing and hemoglobin electrophoreses reported in the medical records were available for 16 and 17 individuals, respectively. Blood from eleven males was tested with both solubility testing and hemoglobin electrophoresis.

Results

Twenty-five males, between the ages of 4 and 40 years presented with splenic syndrome. No females were identified. Two males (8%) were less than 10 years of age, nine (36%) were between 13 years and 17 years, and 14 (56%) were between 18 and 40 years at the time of their splenic syndrome.

Ethnicity data was available for 22 subjects; 9 (41%) were identified as African American, 9 (41%) as non-Hispanic white, and 4 (18%) as Hispanic. Three of the subjects designated as non-Hispanic white were of Mediterranean and one of Algerian descent. Sixteen males (64%) were unaware they had sickle cell trait. By race and ethnicity, 4 of 9 African American (44%), 8 of 9 non-Hispanic white (89%), and 3 of 4 Hispanic subjects (75%) were unaware they had sickle trait.

Twenty-two males resided at sea level and had come to Colorado to visit; three developed pain while skiing, whereas the others did not report onset of pain with exercising. Peak altitude exposures for the 22 non-Coloradan males ranged from 7522–9600 feet; 77% were exposed to 9000–10,000 feet. Their mean altitude exposure was 9000 and median 8932 feet. Three individuals were from the metropolitan Denver area (altitude 5280 feet). The Coloradan subjects were 16, 25, and 32 years old, resided at 5280 feet, and each developed the splenic syndrome after hiking at peak altitude exposures of 10,000, 9000, and 12,000 feet, respectively.

The prevalence of specific symptoms and signs of splenic syndrome are shown in Table 1. Twenty males with available data about time to symptom onset, all developed pain within 24 hours of arrival to peak altitude. In six males, the spleen tip was reported palpable, and two had mild splenomegaly (2–3 cm below the left costal margin). Of those who developed fever, temperatures ranged from 100° to 102.8°F orally.

Laboratory findings are shown in Table 2. Sickle solubility testing was performed and positive for 16 males, indicating sickle hemoglobin was present but not differentiating sickle

TABLE 1. PRESENTING SYMPTOMS AND SIGNS

	<i>Number affected/Number studied</i>	<i>Percentage affected</i>
Left upper quadrant abdominal pain	25/25	100
Vomiting	14/25	56
Fever (>100°F orally)	11/25	44
Oxygen saturation <93% by pulse oximetry	6/25	24
Palpable spleen	8/25	32
Icterus documented in chart	4/25	16
Chest pain	3/25	12
Dyspnea	2/25	8
Testicular pain	1/25	4

cell trait from disease. Hemoglobin electrophoresis was performed on blood from 17 males; Hemoglobin A was greater than hemoglobin S and hemoglobin A2 was normal in quantification. The sickle hemoglobin range was 37.3% to 45%. The results of analyses of beta globin chains by RP HPLC and ESI MS were consistent with the presence of normal hemoglobin A and hemoglobin S. No testing was done for alpha thalassemia. One subject who reported he had sickle cell trait had no confirmatory testing (Table 2, male #18).

As shown in Table 2, of 24 males tested, 70.8% were anemic ($n = 17$), 50.0% had leukocytosis ($n = 12$) and 33.0% ($n = 8$) were thrombocytopenic; two males had platelet counts less than 100,000/ μ L. Total bilirubin was elevated in 94.5% (18 of 19 males) tested.

Seven males were first evaluated with an abdominal x-ray that was normal in five, showed splenomegaly in one, and a splenic tip in the other. A CT scan of the abdomen was obtained in 22 males, and all but one of the scans was abnormal showing splenomegaly, subcapsular hematomas, and/or splenic infarctions. Four males had an abdominal ultrasound; three showed splenic infarct and the fourth showed an abnormal area of hypoechogenicity in the spleen. Eleven males had more than one of the following imaging studies performed: chest x-ray, abdominal x-ray, CT of the abdomen, abdominal ultrasound, abdominal MRI, or liver-spleen scan.

Twenty-two males were admitted to a hospital and three were managed only in the emergency department. The hospitalizations ranged from 1 to 19 days with a mean of 5 days. Conservative treatment for 20 males consisted of transfer to the lower altitude of Denver (5280 feet), intravenous hydration, oxygen, pain medications, and anti-emetics. Six males received intravenous antibiotics. One male received transfusions of red cells and platelets.

Splenectomy was performed in 5 males: 1 for splenic rupture, 1 for hemorrhage requiring platelet and packed red cell transfusions, and another for a concern of malignancy. An explanation for two splenectomies could not be ascertained. Evaluation of the five resected spleens revealed hemorrhage, hemorrhagic infarction, and sinusoidal sickling.

Discussion

Our findings confirm previous reports that the splenic syndrome is associated with sickle cell trait only in males who are exposed to moderate to high altitude (Lane and Githens, 1985, Sheikha, 2005). While we cannot determine the

TABLE 2. LABORATORY RESULTS

Male	Age (years)	Solubility (normal = negative)	% sickle (S) hemoglobin or relative quantity of A and S hemoglobins	Lowest hemoglobin (g/dL)*	Lowest leukocyte count ($\times 10^3/\mu\text{L}$) #	Lowest platelet count (normal 150,000–450,000 $\times 10^3/\mu\text{L}$)	Total bilirubin (normal $\leq 1.2\text{mg/dL}$)
1	4	ND	40	10.8	9.1	242	ND
2	9	+	37.2	12.1	6.8	280	ND
3	13	+	ND	11.4	5.5	148	ND
4	13	ND	40.4	12.7	15.2	153	2.0
5	14	+	ND	13.4	16.0	199	1.1
6	15	ND	39.9	14.4	16.3	160	11.4
7	16	+	37.9	12.3	8.4	182	2.5
8	16	+	40	12.5	11.0	247	ND
9	17	ND	ND	13	13.1	224	3
10	17	+	37.5	10.6	10.7	173	2.7
11	17	ND	39.3	ND	ND	ND	ND
12	18	+	A > S	13.4	10.5	144	2
13	19	+	ND	12.6	10.7	178	3
14	19	+	A > S	11	12.0	156	4
15	20	+	ND	14.1	11.9	133	1.8
16	20	ND	A > S	11.5	11.0	96	3.6
17	22	+	A > S	12	9.70	159	2.4
18	25	ND	ND	10	10.6	27	4.4
19	29	+	ND	11.8	21.7	108	2.8
20	30	ND	A > S	12.4	12.6	156	2
21	32	+	ND	16.1	13.3	“average”	1.5
22	32	ND	42.1	12.9	20.5	101	1.7
23	38	+	A > S	12	14.0	212	5
24	40	+	45	11.4	14.0	117	2.6
25	40	+	40	10	19.3	174	ND

+ = positive; ND = not done; *-2 SD for hemoglobin for age 2–12 years is $\geq 11.5\text{ g/dL}$, 12–18 year males $\geq 13\text{ g/dL}$, and > 18 year males $\geq 13.5\text{ g/dL}$ (Nathan and Oski, 2009); # + 2SD for leukocyte count for age 4 years is > 15.5 ; 9 years > 13.5 ; 16 year > 13.0 ; and 21 years or older $> 11.0 \times 10^3/\mu\text{L}$ (Nathan and Oski, 2009).

incidence of this complication, it appears rare, with less than 100 cases reported since it was first appreciated in the 1940's. The predisposition for splenic syndrome only in males has yet to be determined but has been a consistent finding. Since individuals with sickle cell trait are reported to have more rigid red cells and increased blood viscosity compared with controls, and males greater than 12 years of age generally have a higher red cell number than females, it is possible the two conditions predisposed to the syndrome in the teens and adults but would be unexplained in the children (Connes et al., 2008).

Confirmation of the identity of hemoglobins A and S by chromatographic and mass spectrometric techniques on a subset of males supports the diagnosis of sickle cell trait, as made by conventional hemoglobin separation techniques, making the presence of variant hemoglobin predisposing to the syndrome highly unlikely. Specifically, the ESI MS and RP HPLC analyses ruled out the presence of double heterozygosity for hemoglobin S and Quebec-Chori. Hemoglobin Quebec-Chori is an electrophoretically silent beta globin variant that was reported to cause sickle cell disease in a patient with a sickle beta globin gene (Witkowska et al., 1991).

We found that the symptoms of splenic syndrome occur rapidly, generally within the first 24 hours of arrival to > 7500 feet in altitude in individuals who normally reside at sea level, and 9000 feet or greater for those normally residing at 5280 feet. The symptoms are always located in the abdomen and are typically associated with an elevated total bilirubin. Whereas anemia and leukocytosis are common,

thrombocytopenia occurs in just 33% of those affected. A single imaging study, either ultrasound or CT of the abdomen, is generally adequate for confirming the diagnosis.

In agreement with a previous report (Sheikha, 2005), we found the splenic syndrome generally resolves without surgical intervention if transfer to a lower altitude (in our case 5280 feet) and conservative support is provided. In the absence of documented bacterial infection, intravenous antibiotics are likely unnecessary as splenic function has been shown to be normal even in men with sickle cell trait who chronically reside at 5280 feet (Nuss et al., 1991).

The etiology of the splenic syndrome is unknown but postulated to be vaso-occlusion of the red pulp of the spleen by sickled red blood cells, leading to vascular infarction. Increased red cell rigidity and blood viscosity associated with sickle cell trait may also predispose to the microcirculation obstruction (Connes et al., 2008). Altitude-associated decrease in oxygen tension may exacerbate these abnormalities. Dehydration associated with inadequate water intake for a given altitude in association with underlying hypercoagulability may also contribute to splenic syndrome. Persons with sickle cell trait studied at sea level have been shown to have increased D-dimer, thrombin-antithrombin complexes, and prothrombin fragment 1.2, when compared to AA controls, suggesting increased thrombin generation (Westerman et al., 2002). Coagulation studies have not been studied in persons with sickle cell trait at elevated altitudes. Consistent with hypercoagulability, risk for venous thromboembolism and pulmonary embolism in persons with sickle cell trait has been

shown to be twice that of African Americans with wild-type hemoglobin A (Austin et al., 2007). However, it is important to note, imaging and histopathology of the resected spleens in our study do not demonstrate overt intravascular thrombosis. These unresolved questions suggest research is needed to improve the “medical knowledge base” especially in reference to whether there are “potential genetic modifiers of phenotypic expression” of sickle cell trait that account for development of complications (Goldsmith, 2012).

Although the splenic syndrome was first reported in non-African American individuals, subsequent reports included African Americans (Lane et al., 1985; Frankin et al., 1999). We find a 1.4:1 ratio of non-African Americans to African Americans. It is of note that 44% of the affected African Americans and 85% of the white non-Hispanic and Hispanic males were unaware they had sickle cell trait. With the rapidly growing Hispanic population, which has a 1% frequency of sickle cell trait [www.genome.gov], we predict an increased incidence of splenic syndrome in this population.

Suspicion in males of all ethnicities presenting with acute left upper quadrant abdominal pain shortly after exposure to moderate to high altitude is critical for recognition of the splenic syndrome. A single imaging study, either CT or ultrasound, of the abdomen is confirmatory, and conservative treatment at a lower altitude is generally adequate.

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Address correspondence to:

Jessica Goodman, MD

Center for Cancer and Blood Diseases

Peyton Manning Children’s Hospital at St. Vincent

2001 West 86th Street

Indianapolis, Indiana 46260

E-mail: jfgoodma@stvincent.org

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