CASE REPORT

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Death Due to Microvascular Occlusion in Sickle-Cell Trait Following Physical Exertion

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ABSTRACT: The heterozygous condition characterized by the presence of hemoglobin AS (sickle-cell trait) occurs in approximately 8% of the American black population. Unlike the homozygous state (sickle-cell disease), sickle-cell trait is not widely recognized as a cause of life-threatening illness or death despite over 30 case reports describing fatal or serious complications of exercise in young black males with this condition. These reports identify heat stress, dehydration, viral illness, and poor physical conditioning as factors which may contribute to exertional rhabdomyolysis and sudden death, suggesting multifactorial etiology. However, since sickling is known to occur postmortem, it remains controversial as to whether the pathogenesis of these exercise related deaths involves microvascular obstruction by sickled erythrocytes. We describe three young black individuals with no significant past medical history who died following physical exertion. In all three cases, postmortem hemoglobin electrophoresis demonstrated hemoglobin AS. In none of the cases was the body temperature found to be elevated. These cases serve to remind the forensic community that, in the proper setting, sickle-cell trait must be viewed as a potentially fatal disorder.

KEYWORDS: forensic science, forensic pathology, sickle-cell trait, hemoglobin, sudden death, death, exercise

Sickle-cell trait (AS hemoglobinopathy) is present in over 2.5 million American blacks and occurs with less frequency among those of Mediterranean, Middle Eastern, and Indian ancestry. In contrast to sickle-cell disease (SS hemoglobinopathy), this condition is not widely appreciated as a cause of serious illness or death. However, Kark et al. have shown that recruits in basic training with sickle-cell trait have a substantially increased risk of exercise related death (1). Their retrospective study included all deaths in new military recruits in basic training during 1977 to 1981. The risk of sudden, unexplained death in black recruits with sickle-cell trait was nearly 30 times that in black recruits without sickle-cell trait. The authors identify heat stress, dehydration, viral illness, and poor physical conditioning as factors which may contribute to exertional rhabdomyolysis and sudden death, suggesting multifactorial etiology. In addition, a recent review article details at least 30 cases of fatal or serious complications of exercise in young black males with sickle-cell trait (2). The purpose of this study is to report our experience with exercise related deaths in individuals with sickle-cell trait as seen in a medical examiner's office and to review the literature describing similar deaths.

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Materials and Methods

All cases at the Southwestern Institute of Forensic Sciences in which sickle-cell trait was listed as causing or contributing to death from 1977 to 1996 were reviewed. Those subjects with co-morbidity such as diabetes and anemia were excluded from this study. A complete autopsy and hemoglobin electrophoresis were performed on all cases. Medical records were reviewed in each case. A total of three cases were identified in which AS hemoglobinopathy was listed as the cause of death.

Case 1

A 6-year-old, 40 lb, 3 ft 8 in. black female collapsed while running in the park. Upon arrival to the scene, emergency medical services (EMS) personnel noted lethargy, emesis, normal body temperature and tachypnea; however, no pulse or blood pressure was detected. The child then experienced cardio-pulmonary arrest. Resuscitative efforts were initiated, and she was transported to a local hospital's emergency department (ED) where she was pronounced dead approximately 1 h after EMS arrival to the scene. Several days prior to death, the subject experienced mild "flu-like" symptoms for which she was seen by her pediatrician who recommended fluids and rest. Otherwise, her past medical history was unremarkable. Autopsy demonstrated widespread red blood cell sickling (Fig. 1), as well as sickled erythrocytes occluding scattered vessels within the heart (Fig. 2). Postmortem hemoglobin electrophoresis showed 63% hemoglobin A and 37% hemoglobin S. The heart weighed 99 g. Postmortem toxicology was negative. Vitreous electrolytes were within normal limits.

Case 2

On his first day of training exercises, a 23-year-old, 250 lb, 5 ft 10 in. black male firefighter collapsed after running 1 mile. He sub-

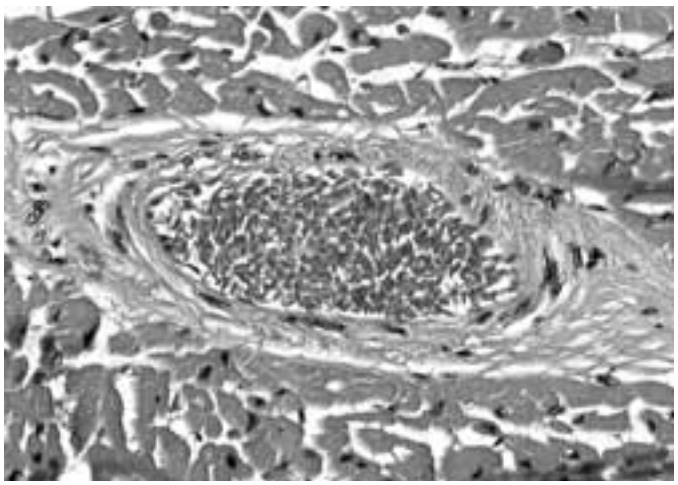

FIG. 1—*Sickled erythrocytes in heart vessel.*

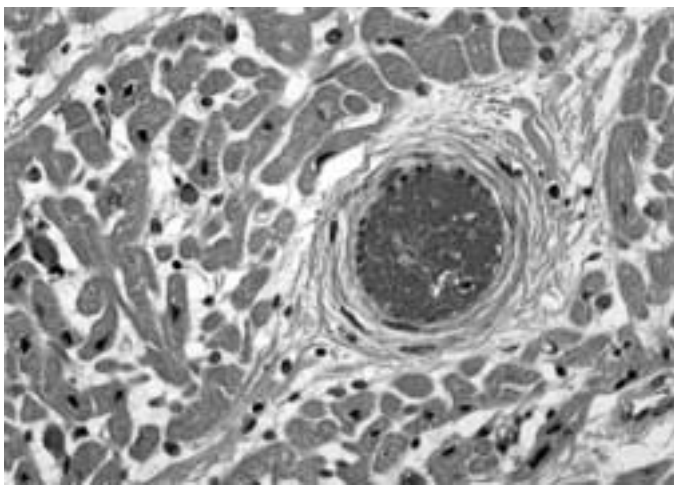

FIG. 2—*Sickled erythrocytes occluding a heart vessel.*

sequently complained of leg cramps and was transported to a local ED in sinus tachycardia. Subsequent evaluation revealed a normal body temperature and a serum creatine phosphokinase (CPK) level of 425 IU/L. His serum sodium and potassium were elevated at 150 mEq/L and 4.1 mEq/L, respectively (chloride = 102 mEq/L, bicarbonate = 7 mmol/L, BUN = 7 mmol/L, creatinine = 2.4 mg/dl, calcium = 10.5 mg/dl and phosphate = 7.4 mg/dl). Following intravenous hydration, his vital signs stabilized and he was admitted with metabolic acidosis and rhabdomyolysis. Approximately 1.5 h after admission, a nurse found the subject on the commode. He had defecated, was drooling and diaphoretic with a pulse in the 80's. He then became pulseless and ventricular fibrillation was noted. Death ensued despite aggressive resuscitative efforts. Prior to initiation of training, the subject led a sedentary lifestyle and was taking erythromycin and a combination drug which contained guaifenesin, phenylpropanolamine and phenylephrine for "bronchitis." Autopsy demonstrated sickled erythrocytes occluding the microvasculature of the heart and kidneys. Sections of skeletal muscle showed rhabdomyolysis. Postmortem hemoglobin electrophoresis showed 58% hemoglobin A and 42% hemoglobin S. The autopsy revealed no evidence of bronchitis or asthma. The heart weighed 400 g. Except for a blood diazepam level of 0.05 mg/L, toxicology was negative. Vitreous electrolytes were within normal limits.

Case 3

A 26-year-old, 194 lb, 5 ft 6 in. black male firefighter failed to complete stair running exercises, complaining of back pain. For the five months prior to this he completed the exercises without difficulty and appeared healthy. He was transported to a local ED where his body temperature was normal. An electrocardiogram showed peaked T waves with normal sinus rhythm. Serum potassium was 5.1 mEq/L. Serum bicarbonate was 11.6 mmol/L and arterial blood gas analysis revealed pH of 7.06. Serum CPK was 235,000 IU/L and a muscle biopsy showed rhabdomyolysis. A drug screen was negative. Despite aggressive therapy, he developed adult respiratory distress syndrome 48 h after admission and required mechanical ventilation. He also developed progressive renal failure with hyperkalemia, arrhythmias and recalcitrant hypotension as well as extensive lower extremity myonecrosis and edema, requiring multiple fasciotomies. Terminally, the patient developed pneumonia, septic shock and multi-system organ failure. He died following a three week stay in the intensive care unit. At autopsy, rhabdomyolysis and bronchopneumonia were confirmed and myocardial and splenic infarcts were discovered. Although the cardiac microvasculature was not occluded by sickled erythrocytes at the time of autopsy, sickled cells were observed within the myocardial and splenic infarcts. In addition, severe renal tubular necrosis was noted. The heart weighed 350 g. Postmortem hemoglobin electrophoresis showed 56% Hgb A, 42% Hgb S and 2% Hgb A2. Postmortem toxicology was not performed.

Discussion

Although AS hemoglobinopathy is demonstrable in a significant number of American blacks, relatively few of these individuals experience life threatening events during physical activity. Previously described risk factors which may contribute to the occurrence of such life threatening events include heat stress, dehydration, viral illness and poor physical conditioning (1). However, there are undoubtedly many persons with sickle-cell trait and one or more of these risk factors who do *not* experience life threatening illness during physical activity. This suggests that there are additional, as of yet unidentified, risk factors which, in combination with underlying AS hemoglobinopathy, are involved in the pathogenesis of this condition.

The pathophysiology of sickle-cell trait is poorly characterized but may relate to microvascular obstruction by sickled erythrocytes. Sickling occurs as a result of polymerization of hemoglobin S when erythrocytes are exposed to acidic environments, increased osmolality, dehydration and hyperthermia (3,4). The pO2 below which sickling occurs in vivo is 45 mmHg (5). Greater sickling is known to occur in individuals when hemoglobin S levels exceed 40% (6). A proposed model, adapted from Kerle (7), is depicted in Fig. 3. According to this model, conditions that shift the hemoglobin oxygenation curve to the right, such as those mentioned above, can initiate a cascade of events leading to sudden death.

Although other reports suggest multifactorial etiology, many fail to consider hyperthermia. Hyperthermia was not present in any of the subjects of this study. Furthermore, the absence of significant co-morbidity in these three subjects with sickle-cell trait implicates their hemoglobinopathy as the underlying cause of death.

This report describes the first exercise related death in a child with sickle-cell trait. Unlike the adults described in various reports

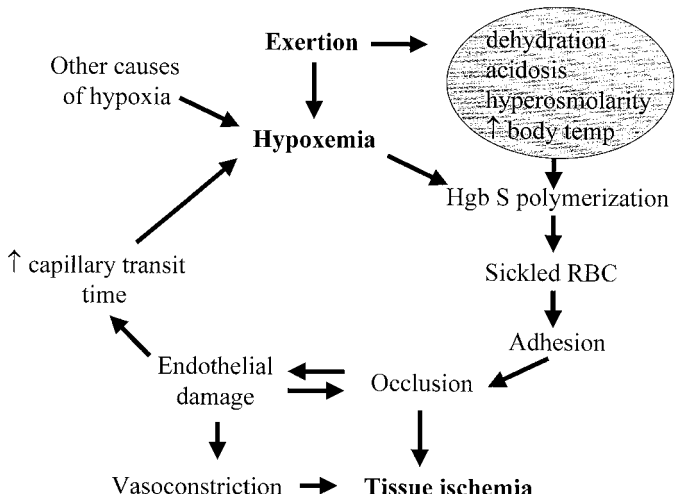

FIG. 3—*Pathophysiologic basis of sickle-cell trait associated sudden death. Modified from a figure in, and used with permission from the October 15, 1997, issue of American Family Physician. © American Academy of Family Physicians. All Rights Reserved.*

and the two young black males in this report, this child with AS hemoglobinopathy did not seem to experience rhabdomyolysis prior to death, suggesting that significant sickling did not occur in the skeletal muscles. Although sickled cells were present at autopsy in histologic sections of lung, spleen and liver, only the heart showed microvascular occlusion by sickled erythrocytes. We feel it is unlikely that these findings represent a postmortem artifact due to the patchy distribution of the occluded vessels as well as the degree of congestion observed in the myocardium. If formalin fixation or terminal hypoxia were responsible for the changes observed in this subject's heart, then these changes should be present uniformly in all organs. This notion is supported by the findings of Dudley et al. who describe vessels containing sickled cells adjacent to vessels containing morphologically normal erythrocytes in the formalin fixed brain of a 34-year-old-black male (8). Furthermore, Ham et al. was unable to induce sickling in erythrocytes containing AS hemoglobin with exposure to formalin or glutaraldehyde (9). Therefore, the presence of sickled erythrocytes in postmortem histologic sections of heart, especially when occluding the microvasculature, should be considered a significant finding. Although there is no direct evidence that these findings are sufficient to cause death, it is possible that the terminal event in these subjects is an arrhythmia triggered by ischemia.

The determination of cause of death in young individuals who die suddenly continues to present many challenges to the forensic pathologist. This problem becomes particularly difficult after a thorough postmortem examination and toxicological studies are unrevealing. In some cases, the cause of death is undetermined. This can only be acceptable if all possible explanations for the demise have been considered. The investigation of deaths in young black individuals and others at risk for AS hemoglobinopathy who die with circumstances similar to those described herein should include postmortem hemoglobin electrophoresis. If demonstrated, AS hemoglobinopathy should be considered as a possible cause or contributory cause of death. In addition, this study raises the question as to whether those at risk in physically demanding occupations should be screened for the presence of hemoglobin S.

Future studies should extend current observations to a large group of subjects with sickle-cell trait to better define the characteristics of individuals at highest risk of potential exercise related morbidity. These studies should include extensive monitoring of cardio-pulmonary function, renal function, electrolytes, and if possible, techniques to evaluate the vaso-occlusive manifestations of sickled erythrocytes (10).

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