Public Health Implications of Sickle Cell Trait
A Report of the CDC Meeting

Althea M. Grant, PhD, Christopher S. Parker, PhD, Lanetta B. Jordan, MD, MPH, Mary M. Hulihan, MPH, Melissa S. Creary, MPH, Michele A. Lloyd-Puryear, MD, PhD, Jonathan C. Goldsmith, MD, Hani K. Atrash, MD, MPH

Abstract: Although the issue of whether sickle cell trait (SCT) is clinically benign or a significant health concern has not yet been resolved, the potential health risk to affected individuals is of vital importance and represents a tremendous challenge in protecting, promoting, and improving the health of the approximately 300 million people worldwide and 3 million people in the U.S. who possess the trait. In response to a request by the Sickle Cell Disease Association of America, in December 2009, the CDC convened a meeting of partners, stakeholders, and experts to identify the gaps in public health, clinical health services, epidemiologic research, and community-based outreach strategies and to develop an agenda for future initiatives. Through facilitated discussion and presentations in four topic areas, participants discussed pertinent issues, synthesized clinical research findings, and developed a coherent framework for establishing an agenda for future initiatives. A primary outcome of the meeting was to provide the first step of an iterative process to move toward agreement regarding appropriate counseling, care, and, potentially, treatment of people with SCT.
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Introduction

On December 17, 2009, the CDC hosted a meeting on sickle cell trait (SCT), inviting partners from the NIH, the Sickle Cell Disease Association of America (SCDAA), the Health Resources and Services Administration (HRSA), and other stakeholders and experts to discuss the scientific and public health implications of SCT. The objective of the meeting was to identify gaps in public health, health services, epidemiologic research, and community-based outreach and to develop an agenda for future initiatives. Specific objectives were to:

- review scientific literature on health outcomes associated with SCT;
- identify opportunities for prevention of adverse health outcomes associated with SCT;
- consider models for screening and health education;
- assess screening programs;
- suggest a framework for screening including health education and follow-up; and
- identify effective strategies for preventing stigma and discrimination.

From the Division of Blood Disorders (Grant, Parker, Hulihan, Creary, Atrash), National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia; Department of Sickle Cell Services (Jordan), the Memorial Healthcare System, Hollywood, Florida; and the Sickle Cell Disease Association of America (Jordan), Baltimore; the Office of Rare Diseases Research (Lloyd-Puryear), NIH, the Division of Blood Diseases and Resources (Goldsmith), National Heart, Lung and Blood Institute, NIH, Bethesda, Maryland

Address correspondence to: Althea M. Grant, PhD, Branch Chief, Epidemiology and Surveillance Branch, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, CDC, 1600 Clifton Road, NE, MS-E64, Atlanta GA 30333. E-mail: agrant@cdc.gov.

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Sickle Cell Trait: Summary of Presentations

To create the foundation for accomplishing the meeting's objective, several speakers were invited to give presentations on a variety of topics. The meeting commenced with a discussion of reports from the medical literature about complications of SCT.[1,2]

Investigations on the prevention of exercise-related mortality for people with SCT were presented that included a discussion of the military experience with interventions and polices to prevent SCT-related deaths among recruits. This was accompanied by a presentation on SCT and athletes, which provided a brief history of the National Collegiate Athletic Association's (NCAA) sickle cell–related policies and statistics on college athlete deaths that occurred between 2000 and 2009.

The final group of presentations focused on various screening programs and models. The NCAA experience with SCT screening among athletes, including the results from surveys of colleges about their participation in SCT testing and their practices in treating athletes for SCT-

related complications, was reviewed.[3,4] Of note, at the time of the meeting, the NCAA was considering a proposal to mandate student screening for SCT unless carrier status was already known. An overview of newborn screening (NBS) policies for sickle cell disease in the U.S. and a summary of practices with respect to the reporting of test results with regard to SCT as well as an overview of recommendations regarding prenatal screening for hemoglobinopathies from the American College of Obstetricians and Gynecologists were presented.[5,6] Finally, a presentation discussing the National Practice Collaborative on preconception health coordinated through CityMatch in Nashville outlined the results of a program designed to address sickle cell education and awareness. The program developed an education campaign that included proposing new policies for school entry and mandatory school physicals at 5th and 9th grades, during which sickle cell status could be determined and discussed.

Because there are few epidemiologic studies examining the association of SCT with exercise-related death or the effectiveness of interventions to prevent exercise-related death among individuals with sickle cell trait, it is important to present here in more detail the evidence accumulated from the experience of the military with regard to SCT testing. Unpublished information was presented that had a strong influence on the discussion and conclusions of the meeting.

Evidence on exercise-related mortality for people with SCT is difficult to definitively classify due to the inability of autopsy findings to determine whether observed sickling of red blood cells post mortem caused an event or was secondary to agonal hypoxia.[7] To address this, researchers adopted a statistical approach comparing the frequency of death among those with SCT and those without SCT from the same population. Studies performed by Dr. John Kark and colleagues at Walter Reed Army Medical Center analyzed nontraumatic deaths during basic training among two million Armed Forces recruits from 1977 to 1981.[7]

Examining the risk of nontraumatic death of African Americans with SCT compared to African Americans and others without SCT, they observed 13 exercise-related deaths in 37,300 recruits with SCT versus five deaths in 429,000 other African-American recruits without SCT, yielding a relative risk of 30. In this analysis, it was observed that half of the cases of death were due to fatal exertional heat illness (EHI) and half were idiopathic sudden death associated with cardiopulmonary arrest. EHI includes exertional rhabdomyolysis with or without hyperthermia, heat stroke, and exertional acute rhabdomyolysis.

At the meeting, Dr. Kark also reported unpublished findings from a prospective interventional trial he directed from 1982 to 1991.[8] This study examined the hypothesis that preventing EHI would reduce mortality for all recruits and in particular the excess risk of death among those with SCT. In this trial, 1.8 million recruits participated in the intervention, and 1.1 million recruits did not. The intervention educated military drill instructors to record physiologic heat index hourly, to decrease training regimens of recruits to minimal effort in hot weather, to order and observe increased water consumption, to have recruits exercise in light clothing unless special exercises prevent this, and to get an immediate rectal temperature and initiate rehydration if a recruit showed early signs of "falling out" from group training. Although 13 deaths were expected among SCT recruits if no interventions were enforced, no deaths were observed when the precautionary measures were undertaken. This was a significant decline in predicted mortality by about 22-fold ($p<0.01$). It was calculated that there were also six lives saved among those without SCT due to the interventions.

In the nonparticipant group, there were four exercise-related deaths among individuals with SCT, all during hot weather, which correlated with the expected number of deaths. The conclusion was that reducing the number of deaths does not require screening for SCT when the same prevention methods are universally applied, and EHI is a necessary and preventable factor contributing to sudden exercise-related death with SCT. In a separate analysis, Dr. Kark found that the risk of mild to moderate EHI among Marine recruits at Parris Island during the same time period was the same for those with SCT and without SCT. Thus, it appears that SCT does not affect EHI until it becomes life-threatening. This was contrary to the expected results.

Additionally there was a discussion of the evolution from the late 1960s to the present of the military's policy relative to hemoglobinopathy screening. The U.S. Department of Defense (DoD) has concluded that the evidence supports SCT as a risk factor for EHI, likely with a contribution from still-unidentified genetic polymorphisms, but that risk can be reduced by prevention measures such as modified training practices. Individuals must meet specific medical fitness standards to qualify for entry into active duty in the Armed Forces. Currently, SCT is not a disqualifying condition for entry into the Armed Forces. However, anemia that can not be corrected by therapy is a disqualifying condition for military service, and with respect to hemoglobinopathies, sickle cell disease (SCD), not SCT, is frequently the cause of the uncorrectable anemia that disqualifies individuals for service. The 2003–2004 Armed Forces Epidemiological

Board (AFEB) recommended that all applicants be screened for anemia (defined as hemoglobin <13.5 g/dL for men and <11 g/dL for women) and tested for hemoglobinopathies if anemia is present. Eligibility for military service is based on a history of anemia as reported by the applicant on their medical history form, not SCT status.[9]

Although SCT does not exclude individuals from joining the armed services, depending on the branch of armed services, recruits may be screened for SCT once they have joined the military. The Army does not screen recruits for SCT, although soldiers being considered for certain high-risk occupations (e.g., aviation, diving, and special operations) are screened, and those with SCT may be considered medically unfit for participation in those activities. The Air Force, Navy, and Marines screen recruits upon entry into basic training for SCT. Group counseling of individuals who screen positive is routine. The Navy and Marines require recruits with SCT to wear identifiers during basic training. The Air Force allows recruits with SCT to leave service if they choose. All branches have heat injury prevention policies in place for all trainees. Additionally, all military branches also screen all babies born to military personnel for sickle cell and other hemoglobinopathies as part of newborn screening.[10]

Conclusions and Recommendations

After each speaker, meeting participants highlighted the public health needs with respect to SCT in the U.S. and identified approaches to address these gaps. The areas discussed included epidemiologic and clinical research, community awareness and education, ethical and legal concerns, screening practices, and prevention of adverse health outcomes.

Research in Sickle Cell Trait

The meeting participants expressed concern that there was a lack of both evidence and systematic evaluation of evidence to assess risks of adverse health outcomes associated with SCT. Meeting participants commented that researchers should not rely on the use of the general population with different ethnic backgrounds as controls in case-control studies and should determine whether exposures are the same between cases and controls. Another methodologic issue noted in SCT studies included the failure to fully consider the effect of confounding variables and comorbidities. An example is the failure to consider the impact of genetic modifiers such as α-thalassemia trait. Participants identified the need for further research to improve understanding of several SCT issues including:

- the prevalence of SCT among athletes to accurately determine the rate or risk of adverse health outcomes;
- the incidence of exercise-related adverse health outcomes (ERAHOs) associated with SCT. In addition to exercise-related deaths, there may be other ERAHOs that are not well documented.
- the impact of preconditioning, heat acclimatization, work–rest cycles, proper hydration, and clothing on those with SCT;
- the pathophysiologic mechanism of the association of SCT with ERAHOs;
- the psychosocial effect of targeted screening on individuals; and
- the impact of SCT on less studied outcomes such as adverse pregnancy outcomes, venous thromboembolism, and others.

In addition, participants identified several resources needed to facilitate addressing SCT research questions. These include:

- longitudinal cohort genetic studies;
- databases that provide a sufficient population size to provide study power to analyze the impact of SCT;
- studies that assess the influence of comorbidities, environmental factors (e.g., altitude), and genetic and biological factors (e.g., hemoglobin S level, haplotype, α-globin genotype) on risk of ERAHOs of individuals with SCT;
- systematic analysis of current evidence supporting the association of SCT with adverse health outcomes;
- studies that improve understanding of the etiology of ERAHOs associated with SCT;
- studies to distinguish causality from association;
- research on exercise (potential and limitations) for those with SCT; and
- cross-disciplinary collaboration on research.

Communication, Education, and Awareness

The participants expressed concern that there was a lack of consistency in content and delivery of health education messages about SCT and a lack of public awareness regarding the health issues associated with SCT. Participants noted that translating medical terminology for families is difficult, particularly in a period of declining outreach/education resources. However, some resources already exist. For instance, HRSA funded several years of research and development to support communicating complex genetic messages across languages and cultures, and participants suggested that the educational materials and documents produced from those projects could serve as a resource. Additionally, the experience of the former national network of sickle cell centers can provide some "lessons learned" on reaching the community. With respect to counseling, participants noted that information

about SCT is not a one-time message from care providers; it must be repeated at various stages of life so that people have the information at times when it is most useful to them. The participants suggested the following activities are needed to move the community awareness and health education initiatives forward:

- Health education efforts should capitalize on existing resources that have been created by established organizations and/or funded by federal agencies such as HRSA.
- Education and awareness about risks associated with SCT targeted toward policymakers, general public, media, health providers—especially primary care providers—coaches, and employers and addressing needs of various populations should be improved.
- Awareness and education strategies that incorporate broad media sources and community institutions, including faith-based organizations, schools, daycare, and other community institutions, should be developed.
- Health education efforts should address variability in health literacy, cultural and linguistic diversity, and reproductive decision making, as well as adverse health outcomes for individuals.
- Health education efforts should avoid increasing stigma and unduly worrying parents/athletes/prospective parents. It was noted that it is important to inform individuals aware of their SCT that they can still choose to participate in athletics. Institutions with appropriate standards of care and training in place can minimize the risk of adverse outcomes.
- Uniform consistent SCT messages should originate from authoritative public health sources such as the CDC, HRSA, NIH, and others.
- Programs are needed to support public understanding of genetic information. Participants suggested that health education messages may need to be tailored for SCT. Participants mentioned that traditional teaching about recessive disorders implies that there is no risk of adverse health outcomes among carriers, but this may not be the case with SCT, and consideration of this is needed when selecting the terminology used in SCT education.

Screening Practices

The participants expressed concern that only reliable laboratory methods (i.e., hemoglobin electrophoresis, high-performance liquid chromatography, or DNA-based techniques) should be used for screening in order to support appropriate individual education for all abnormal hemoglobins, not just hemoglobin S. Although the cost of screening is a potential barrier, participants cautioned against the utilization of less expensive solubility tests as a part of screening programs. The participants stated false-negative results from these types of tests may lead to incorrect reassurances, including the risk of having a child with SCD or another hemoglobinopathy. The participants suggested the following are needed to address screening issues:

- accurate and cost-effective means of ascertaining trait status, including new cost-effective molecular tests and a system to make NBS results available to physicians, parents, and affected individuals throughout the lifespan of the individual;
- easy-to-read, informative, and consistent screening reports;
- adequate funding to implement uniform screening and follow-up programs (especially NBS follow-up at the local level); and
- an informed testing process, including consent to screening and appropriate genetic counseling.

Ethical and Legal Concerns

The participants expressed concern that even in the context of organized sports, athletes with SCT could experience discrimination. For example, institutions might protect athletes with SCT and the institution from litigation by excluding affected athletes from practice. Participants voiced concern that some athletes have lost their athletic scholarships due to this issue. Participants also suggested that only a neutral informed party, such as a physician or genetic counselor, should provide screening results and communicate the health implications of having SCT to an individual. Additionally, there was discussion about the implications of SCT and regulations to protect individuals against genetic discrimination using legislation such as the Genetic Information Nondiscrimination Act (GINA) of 2008.[11] Participants expressed concern that screening for SCT may lead to a focus on the primary prevention of SCD. The participants cautioned that although it is important to address concerns for those with SCT, care is needed to avoid diverting funds to SCT away from efforts to deal with SCD health issues that remain as an underserved area of health care and public health. The participants suggested the following are needed to address ethical and legal concerns regarding SCT:

- Policies that minimize discrimination, exclusion, and stigma based on SCT status: Special attention is needed to avoid unintentional discrimination or bias from "labeling" people with SCT. In addition, policies need to be universal to avoid potential for racialization and stigmatization of athletes, in particular for African Americans with SCT.
- Policies that protect privacy: Although it is important that individuals know their carrier status, care must be taken to develop policies and procedures to protect

privacy of screening information. This may particularly be an issue if programs are implemented to minimize redundant screening by broadening legal access to universal NBS data.
- Research that monitors ethical, legal, and psychosocial results of screening programs: Participants suggested a research component that would track medical, legal, and psychosocial outcomes for identified individuals.

Prevention

To prevent adverse health outcomes, particularly exercise-related health events for individuals with SCT, most participants expressed support for utilizing a universal precaution approach in athletic training similar to DoD's interventions for EHI. This approach has been demonstrated by the military to reduce exercise-related deaths among those with SCT even in the absence of SCT screening. However, participants also noted that the athletic culture makes "universal precautions" difficult to implement. Others cautioned that relying on screening alone may not be sufficient to protect athletes and that implementation of screening guidelines may be inconsistent.

Several opportunities for prevention of adverse outcomes of SCT were identified:

- universal safe training practices for all athletes;
- collaboration of the public health community with the National Football League or collegiate athletic associations on primary and secondary prevention of ERAHOs;
- provision by the states of universal follow-up and education of carriers and creation of a database of that information that is accessible to screened individuals and their healthcare providers;
- the use of a comprehensive standard sports physical examination and history that is consistent in quality and ensures that information is passed on to adolescents before the adolescent is at risk;
- tools and education materials available for people with limited English proficiency and varying levels of health literacy;
- systems for adults to be screened and to have access to that information;
- standard policies for organizations to screen for all hemoglobinopathy traits, not just SCT, so that the athletes and others will understand their risk of having children with SCD;
- uniform availability of genetic counseling for those screened; and
- models that are tailored to the cultural contexts of organizations and populations served.

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