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Sickle Cell Trait: What Every Nurse Practitioner Should Know

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ABSTRACT

Sickle cell trait is a carrier state for the β-chain sickle hemoglobin mutation. Individuals with sickle cell trait have normal life expectancy and no symptoms of sickle cell disease, with the exception of some rare but serious complications such as renal abnormalities, venous thromboembolism, and exercise-related injuries. Sickle cell trait has important reproductive consequences, with a risk of having a child with sickle cell disease. Nurse practitioners should be aware of the screening, potential complications, and routine management of individuals with sickle cell trait in order to provide evidence-based care to this population.

Keywords: exercise-related rhabdomyolysis, exercise-related sudden death, genetic counseling, newborn screening, renal medullary carcinoma, sickle cell disease, sickle cell trait

Sickle cell trait (SCT) is the most common genetic mutation of hemoglobin. An individual with SCT inherits 1 mutated sickle β-chain hemoglobin gene from the mother or father, with a nonmutated gene from the other parent (heterozygous variant). Acquisition of 2 abnormal sickle genes from both parents (homozygous variant) leads to sickle cell disease (SCD).[1] In heterozygous SCT, normal (hemoglobin A) and abnormal sickle (hemoglobin S) hemoglobin are both produced, whereas only hemoglobin S is present in homozygous SCD.[1] The sickle gene can also be inherited along with other β-chain gene variants, such as hemoglobin C (hemoglobin SC disease) or β-thalassemia (sickle β-thalassemia).[1] These sickle cell variant syndromes have variable clinical presentations but are generally less severe than SCD. Because SCD is an autosomal recessive disorder, parents who both are heterozygous SCT carrier status have a 25% chance of having an offspring with SCD with each pregnancy. This risk increases to 50% if one of the parents has SCD and the other has SCT.

Individuals with SCT are generally asymptomatic and enjoy typical life spans, and yet, may experience uncommon but serious health complications and transmit the sickle gene to their children.

EPIDEMIOLOGY

According to World Health Organization estimates, 5% of the global population carries the SCT, with the highest rate of individuals with SCT (20% to 40%) rising from the regions of Sub-Saharan Africa, the Middle East, the Mediterranean region, and India.[1] In areas where malaria occurs frequently, SCT offers some protection against severe infection caused by a malaria parasites, especially by *Plasmodium falciparum*. This is believed to be a major reason for genetic continuation of the sickle hemoglobin mutation.[1]

The historical trans-Atlantic slave trade and other factors led to distribution of the mutated hemoglobin gene to other areas of the globe.[2] The Centers for Disease Control and Prevention reports that 1 in 13 black Americans (8%) have the SCT and about 100,000 Americans, primarily of African ancestry, live with SCD.[3] Accurate prevalence of SCT is challenging to determine due to inadequate data reporting.

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PATHOPHYSIOLOGY

SCT is a heterozygous carrier state, not a disease. In SCT, sickle hemoglobin S accounts for only 35% to 45% of total hemoglobin.[1] The presence of normal hemoglobin A dilutes mutated hemoglobin S and greatly reduces the probability of sickling and hemolysis.[1] However, erythrocytes stiffness, increased blood viscosity, and intravascular thrombosis have been reported in individuals with SCT in situations of severe volume depletion, hyperthermia, and reduced oxygen tension.[4] In extreme circumstances of high-intensity sports and military training, SCT has been shown to increase the risk of rhabdomyolysis and exercise-related sudden death.[4] Structural changes of red blood cells and impaired endothelial function account for other rare SCT complications such as venous thromboembolism and kidney damage. However, the magnitude of the clinically relevant red blood cell sickling and intravascular thrombosis is much less in SCT persons than in SCD patients.[2] For these reasons, SCT individuals do not display chronic vaso-occlusive complications and have a life expectancy similar to that in general population.

Hemoglobin S is a predominant type in SCD, and normal hemoglobin A is absent. When exposed to conditions of low oxygen, red blood cells, containing hemoglobin S, become inflexible and assume a sickle shape.[1] Chronic sickling, vaso-occlusion, and hemolysis are hallmarks of SCD.[1] SCD affects every major organ system, causes significant morbidity, and reduces the life span of the affected individuals by almost 30 years. [5]

SCT SCREENING AND GENETIC COUNSELING

Screening of Newborns

Fifty states in the United States offer SCD screening at birth and the proportion of parents opting out of screening is low.[6,7] The screening is performed to identify newborns with SCD so that appropriate care can be initiated as soon as possible. In the course of screening for SCD, SCT carriers are also identified. Because detection of SCT is not the primary purpose of the newborn screening, some laboratories may not convey the SCT finding directly to parents, and therefore, parents of children with SCT may be unaware of their infant's screening results.[8]

If results indicating the presence of SCT are not directly reported, the opportunities to counsel families on potential SCT—related complications and future family planning might be overlooked. Knowledge of their SCT status may affect life style and reproductive choices not only of the newborn at puberty and beyond but also of the parents, other children of the parents—full and half-siblings, and extended family members.[9]

Nurse practitioners (NPs) should therefore carefully document newborn screening results in medical records and communicate this information to the patients. Families of children identified with SCT should receive verbal and written information that clearly differentiates between SCT and SCD and reinforces the potential reproductive and family planning implications for the entire family.[9] NPs caring for pediatric patients should redisclose SCT status to their patients of reproductive age. Referral for formal genetic counseling is recommended.

Screening of Adolescents and Adults

Despite widely performed newborn screening, some individuals who were born before routine screening implementation or immigrants from countries without screening may not have been screened at birth. Many others may not be aware of their SCT status because of inconsistency in reporting. A survey of African American young adults found that 52% of participants were uncertain of their personal SCT status.[10] Although there are no studies indicating that SCT status awareness decreases adverse health consequences in people with SCT, information about SCT may be beneficial in many life situations such as family planning and participating in intensive military or athletic training. SCT status disclosure may be used as an educational opportunity to assist individuals in making better decisions to support health and avoid harmful situations. Therefore, NPs should offer SCT screening to asymptomatic adolescents and adults who may benefit from this information.

Ethnicity should not be used as a criterion to offer screening, given the increasing diversity in ethnic distribution of the SCT. The benefits of screening should be weighed against potential harms, such as psychological distress, misinterpretation of the carrier

status, and possible insurance, employment, and marriage discrimination.[8] The decision to screen should be patient-centered, and screening should be linked to meaningful counseling.

Screening of Military Personnel

There is no universal requirement for SCT screening in the military, and screening practices of military service personnel vary by service branch. The US Army does not require universal SCT screening, whereas the Air Force, Marines, and Navy continue to use screening protocols for SCT at enlistment.[8] The Army maintains practices to diminish the risk of exercise-related illness for all soldiers, irrespective of their SCT status.[11] Universal precautionary measures that prevent dehydration and physical exhaustion have been shown to decrease exercise-induced death in all soldiers, including those with SCT.[11]

Screening of Athletes

The National Collegiate Athletic Association asserts that SCT is not an impediment to competitive sport participation but recommends SCT status verification for all student athletes.[12] The American Academy of Pediatrics, American Society of Hematology, and the Sickle Cell Disease Association of America contest SCT status confirmation due to a concern that SCT-positive athletes would be discriminated against based on their SCT status and could be denied sport participation and athletic scholarships.[8] Instead, they recommend establishing universal precautions to the benefit of all student-athletes without requiring disclosure of the athletes' SCT status and, therefore, minimizing the risk of discrimination.[8]

Prenatal Screening

The American College of Obstetricians and Gynecologists endorses SCT screening for all pregnant women.[13] The rationale for prenatal screening is to identify individuals whose offspring are at risk for SCD. If the screening results demonstrate that the mother is a SCT carrier, then paternal evaluation is needed to adequately assess fetal risk.[13] Fetal diagnosis via chorionic villus sampling may be offered to pregnant couples (if both partners are carriers) to determine whether the fetus has SCD and allow parents to make reproductive choices based on this information.[13]

Despite these recommendations, however, prenatal screening and fetal diagnosis raise serious ethical concerns because the clinical phenotype of the affected infant is difficult to predict, and a parental decision about pregnancy continuation strongly depends on the gestational age at diagnosis.[14] Confirmed fetal SCD does not alter obstetrical care in most cases, as this condition typically has no adverse effects on the fetus, mother, or course of pregnancy.[14]

SCT Genetic Counseling

Disclosure of positive SCT should be accompanied by genetic counseling conducted by a genetic counselor or knowledgeable practitioner.[15] Genetic counseling is particularly important at 3 major life course points: early infancy—when newborn screening results may affect future siblings; adolescence—when intensive athletic training may be initiated; and early adulthood—when family planning decisions become important.[15] During a counseling session, information regarding the specific meaning of the recessive trait, the risk of a few very rare SCT-related complications, and the risk of having an offspring with SCD should be conveyed. The individual with SCT should be encouraged to discuss SCT within their own families and with their reproductive partner, who should be offered screening and counseling. The information about an individual genetic risk and reproductive options (eg, preimplantation diagnosis of embryos retrieved during an in vitro fertilization, prenatal diagnosis, partnering with an individual with normal hemoglobin) should be delivered without providing any specific recommendations about the best course of action, thus acknowledging that an individual's decision is dictated by personal preferences.

SCT COMPLICATIONS AND CONSIDERATIONS FOR PRACTICE

Although SCT is generally regarded as a benign carrier condition, current evidence suggests that SCT is associated with relatively uncommon complications. Due to the large number of SCT individuals, NPs should be aware of these potential health sequelae. NPs should encourage SCT individuals to disclose/redisclosure their carrier status at every

health care encounter, including primary care, emergency department visits, and surgical clearance. The Table outlines SCT complications and practice considerations.

Exercise-Related Injuries

Routine physical activities do not pose health risks. Concerns have been raised about a higher risk of exercise-induced sudden death and rhabdomyolysis that occur in SCT individuals when exposed to conditions of extreme physical stress.[8] These complications have been reported in military recruits and elite athletes when hypoxia within anaerobic skeletal muscles leads to massive sickling, multi-organ damage, and death. A retrospective cohort study of 47,944 black American soldiers revealed that SCT increased a risk of rhabdomyolysis—but not death—with strenuous physical activity.[11] These data support the practice in the military of using precautionary measures (slow build-up of exercise intensity, sufficient time for rest, and adequate hydration) in all soldiers, regardless of their SCT status. Maintaining these precautions has been demonstrated to decrease exercise-related mortality in SCT.[11]

NPs should counsel SCT individuals regarding their elevated risk and reinforce the importance of precautionary steps to prevent dehydration, hyperthermia, and exhaustion during intense physical activity. However, athletes often do not design their own training routines. There is also a predominant

Table. Sickle Cell Trait Complications and Management Considerations

Complication	Preventative Measures and Management Considerations
Chronic kidney disease	• Consider screening of SCT individuals for CKD with serum creatinine and urine albumin
Renal medullary carcinoma	• Evaluate SCT individuals with unexplained and persistent hematuria with renal imaging studies (computed tomography or intravenous pyelography)
Asymptomatic hematuria	• Exclude renal neoplasm, glomerular disease, infection, nephrolithiasis, and trauma in SCT individuals with persistent gross hematuria
Exercise-induced complications	• Advocate for universal precautions for all athletic programs • Counsel SCT individuals participating in exertional activities: ➢ to gradually buildup performance levels ➢ allow adequate time for rest ➢ maintain adequate hydration ➢ stop any activity with onset of muscle cramping and fatigue
Splenic infarct	• Counsel SCT individuals traveling to high altitude: ➢ to ascend gradually ➢ allow sufficient time to acclimatization ➢ avoid dehydration and exertion • Suspect splenic infarct in SCT individuals travelling to high altitude if they exhibit a sudden onset of left-sided abdominal pain • Treat splenic infarct with supportive measures (eg, changing altitude, hydration, analgesics)
Traumatic hyphema	• SCT patients with traumatic hyphema should be immediately referred to ophthalmology care
Pulmonary embolism	• Counsel SCT individuals about a risk of VTE • Counsel SCT airline travelers frequently ambulate and perform leg exercises while seated • Consider anticoagulation in special settings (eg, surgery, acute medical illness for which thromboprophylaxis is indicated)
Reproductive risk of having a child with SCD	• Encourage SCT individuals to disclose SCT status to family members and reproductive partner • Encourage family members of SCT individuals to be screened • Refer to genetic counseling

CKD = chronic kidney disease; SCD = sickle cell disease; SCT = sickle cell trait; VTE = venous thromboembolism.
Adapted from Centers for Disease Control and Prevention,[16] 2018; Naik and Haywood,[6] 2015.

competitive sport culture by which athletes are pushed beyond their limits, and those who cannot keep up are not given the same opportunities.[8] Therefore, responsibilities for enforcing universal precautions should be placed on personnel overseeing athletic activities, including NPs. Creating universal policies with a focus on safety of all athletes, including those with SCT, should be an important priority of NPs.

Renal Complications

Renal dysfunctions are the most common SCT-related complications.[8] Physiologic medullary hypoxia and sluggish blood flow through the renal medulla promote overt sickling and contribute to the particular vulnerability of the kidney.[8] The prevalence of asymptomatic hematuria and decreased ability to concentrate urine is higher in individuals with SCT than in those with normal hemoglobin.[2] Renal medullary carcinoma, a rare and aggressive tumor with a poor prognosis, occurs almost solely in young SCT individuals.[2] NPs should promptly evaluate SCT patients presenting with unexplained hematuria and flank pain. Diagnostic imagining is needed for timely identification of renal malignancies.

Recent research has established an association between SCT and chronic kidney disease, with an approximate risk of 6%.[17] Because black individuals have a disproportionally greater risk of kidney dysfunctions compared with other ethnicities, SCT may be viewed as an important, previously unknown, risk factor of chronic renal insufficiency in this patient population. At present, there is no therapy that prevents the progression of nephropathy specific to SCT. Testing for SCT in patients with renal abnormalities is of unclear benefit.[2] NPs may consider periodic monitoring of asymptomatic SCT carriers with serum creatinine, glomerular filtration rate, and urine albumin, with further evaluation based on the results.

Venous Thromboembolism

Venous thromboembolism (VTE) has been reported in SCT individuals.[8] Low oxygen tension within venous valves of the lower extremities may predispose to overt sickling and increased coagulation activity.[18] In a large general population cohort of 30,424 individuals, the risk of VTE and, in particular, pulmonary embolism was 2-times higher in SCT individuals than in people with a normal hemoglobin variant.[18] A similar risk has been described in hospitalized patients with SCT.[7] Currently, there are no data on the benefits of routine SCT testing as part of the thrombophilia workup in patients presenting with VTE; however, it appears prudent to consider SCT as a possible risk factor for VTE and counsel individuals with SCT about avoiding conditions that may increase thrombotic risk (eg, prolonged immobility). NPs should consider prophylactic anticoagulation for SCT patients in specific clinical situations (eg, surgery, acute medical illness), especially if they have a strong family history of VTE or other VTE risk factors.

Pregnancy-Related Considerations

The presence of SCT does not elevate a risk of pregnancy-related complications in affected women. In a cohort study with more than 20,000 black women, SCT carrier status did not increase perinatal death rates or the risk of preeclampsia.[14] Although gestation is known to increase hypercoagulability, an epidemiologic study of 12,000 pregnant women found that SCT did not further raise the risk of VTE during pregnancy.[19]

Vaso-Occlusive Events

Splenic infarct is an uncommon complication of SCT occurring in the setting of reduced oxygen tension at high altitudes while climbing mountains.[8] Splenic infarcts are usually minimally symptomatic and self-limiting.[8] The presenting symptom is left upper-quadrant abdominal pain. Most cases of splenic infarction can be adequately treated with lowering altitude, sufficient hydration, and analgesia, although splenectomy may be needed in severe instances.[8] NPs should counsel SCT travelers to high altitude to maintain precautionary measures such as ascending gradually, allowing sufficient time for acclimatization, and limiting exertion.

Priapism has also been reported in SCT carriers,[8] although there is a lack of evidence to confirm this association. In published case reports, priapism occurred in the setting of other potential precipitating factors, such as cocaine use.[8]

SCT individuals are at higher risk for traumatic hyphema (ie, collection of blood in the anterior eye chamber due to injury), with a subsequent elevation in intraocular pressure and a risk of vision loss. Individuals with SCT who develop traumatic hyphema should be immediately referred to ophthalmology care. NPs should counsel SCT people about importance of seeking medical attention for eye injuries or severe abdominal pain that occurs when travelling to high altitude areas.

Cardiovascular Risk

Underlying hypercoagulability with SCT has been proposed as a concerning factor, but there has been no evidence thus far to support an association between SCT and cardiovascular complications.[8] A recent meta-analysis that included more than 19,400 participants demonstrated no greater risk of ischemic stroke in people with SCT.[20] Other studies reported no increased odds of heart failure, hypertension, diabetes, or metabolic syndrome in people with SCT.[4] This evidence offers some reassurance that SCT does not elevate the risk of cardiovascular and cerebrovascular complications.

MANAGEMENT CONSIDERATIONS

Individuals with SCT should be managed similarly to the general population. However, NPs should be aware of some unique issues that may arise while caring for SCT individuals. Referral to the SCT toolkit developed by the American Society of Hematology together with the Centers for Disease Control and Prevention and the Sickle Cell Disease Association of America should be offered.[16]

Appropriate Laboratory Tests for SCT Screening

SCT cannot be identified on routine complete blood count or peripheral blood smear. Levels of hemoglobin and hematocrit, reticulocyte count, and erythrocytes indices (eg, mean corpuscular volume, mean corpuscular hemoglobin concentration) are within normal reference ranges in SCT. The SCT can be detected using hemoglobin electrophoresis, isoelectric focusing, or high-pressure liquid chromatography.[9] In SCT, as opposed to SCD, both hemoglobin A and hemoglobin S are found, with the percentage of hemoglobin A (60%) greater than hemoglobin S (40%).[1] Levels of hemoglobin S may be lower and difficult to detect in the presence of fetal hemoglobin in newborns.[1] Repeat testing in 6 months (when production of fetal hemoglobin decreases) or DNA analysis can be used to establish SCT.

Evaluating Hematuria

Microscopic and macroscopic hematuria is common in SCT. The exact etiology of blood in the urine is unknown but is thought to be related to intravascular thrombosis in the renal medulla.[1] In rare circumstances, hematuria maybe a manifestation of renal medullary carcinoma.[8] NPs should thoroughly evaluate SCT patients presenting with hematuria. SCT-associated hematuria is a diagnosis of exclusion, and ruling out glomerulonephritis, urinary tract infection, nephrolithiasis, and malignancy is required before attributing the bleeding to SCT. Referral to nephrology or urology specialists is warranted.

Screening for Diabetes

Although not associated with diabetes, SCT may affect hemoglobin A1C (HbA_{1c}) measurements. There has been growing evidence that the HbA_{1c} reading may underestimate the glucose level in individuals with SCT, which may affect diabetes diagnosis and monitoring.[21] Because African Americans have an above-average prevalence of diabetes and diabetes-associated complications, the cost of inaccurately assessing the glucose level is high.[21] NPs should recognize that SCT may affect HbA_{1c} levels and consider performing oral glucose tolerance or fasting glucose tests in individuals with SCT.

Blood and Stem Cell Donation

Individuals with SCT can donate blood for the general blood supply and can serve as donors for solid organs and for hematopoietic cell transplantation.[3] NPs should encourage people with SCT to consider registering as potential organ and tissue donors.

Birth Control

It is well known that combined oral contraceptives may raise a risk of thromboembolic events. However, this risk is not further increased in those contraceptive users who also have SCT.[19] The use of combined

oral contraceptives is not contraindicated in women with SCT or SCD for this matter. Thus, NPs should not limit birth control options for SCT carriers with no other risk factors for VTE.

REDUCING THE INCIDENCE OF SCD

Offering SCT screening and educating the public about SCT genetic risks may present an opportunity to affect reproductive behaviors and reduce the occurrence of SCD.[9] Knowledge of SCD inheritance is necessary for making informed choices concerning reproductive health.[22] Increasing the number of young men and women who are aware of their SCT status and understand SCT genetic vulnerability may possibly reduce the number of children inheriting SCD.[15] Despite availability of screening programs, the acceptance of screening tests and public knowledge of inheritance of SCD remains lower than desired. Community-based surveys have consistently demonstrated limited awareness and understanding of SCD and SCT among African Americans.[10]

One of the barriers to information uptake maybe a lack of trust in health professionals, often because of previous unfair and unethical medical treatments.[23] Population screening programs of 1970s were often designed as targeted screening of African Americans, and several jurisdictions enacted laws requiring black individuals undergo screening for SCD.[23] Because of their insensitivity to race-related concerns, these programs resulted in discrimination against African Americans.[23] In certain states, school attendance and marriage licenses were precluded as a result of unwillingness to undergo screening.[23]

Meaningful changes have been made to improve screening practices; however, mistrust continues as an issue when it comes to SCT/SCD screening and education. To overcome this barrier, NPs should collaborate with trusted community leaders and faith-based organizations for help in delivering information that is ethnically and culturally sensitive.[23] Such organizations can also encourage persons to be tested for SCT and to be more open to disclosing SCT status to their partners and families. By partnering with community groups, NPs can improve public awareness and knowledge, and thus, potentially decrease the incidence and the healthcare burden of SCD.

CONCLUSION

SCT is carried by 5% of the global population. Carrier status increases the risk of having an offspring with SCT, and if the partner also has SCT, SCD. Although SCT was long been considered as benign, knowledge is accruing of uncommon but potentially severe complications associated with the SCT carrier status. Despite these associations, the life expectancy of people with SCT is similar to the general population. However, with the high prevalence of SCT, it is important that NPs be aware of these comorbidities. Through appropriate screening, education, referral to genetic counseling, and intervention, NPs may mitigate some of these complications and improve health outcomes for individuals with SCT. JNP

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1555-4155/18/$ see front matter

https://doi.org/10.1016/j.nurpra.2018.07.020