minireview

Epidemiology of sickle cell disease in Saudi Arabia

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Sickle cell disease (SCD) is an autosomal recessive disorder characterized by production of abnormal hemoglobin S and is associated with high morbidity and mortality. Information about the prevalence of SCD in Saudi Arabia is patchy and probably underestimated, but studies have reported that SCD is a relatively common genetic disorder in this part of the world. The prevalence of SCD in Saudi Arabia varies significantly in different parts of the country, with the highest prevalence is in the Eastern province, followed by the southwestern provinces. The reported prevalence for sickle-cell trait ranges from 2% to 27%, and up to 2.6% will have SCD in some areas. Clinical and hematological variability exists in SCD in Saudi Arabia with two major phenotypes: a mild phenotype and a severe phenotype. Further studies on the prevalence, molecular and clinical epidemiology of SCD may help predict disease severity and risk stratification of patients to determine whether to receive early intensive care or continued symptomatic care.

Sickle cell disease (SCD) is one of the most important single gene disorders of human beings. In the United States, SCD affects about 72 000 people and 2 million are carriers.[1] In Africa, more than 200 000 infants are born yearly with SCD.[2] In the United States, mortality has decreased dramatically with newborn screening and better comprehensive care. The median age of death in patients with SCD in the United States is now 53 years for men and 58 years for women.[3] However, SCD patients are still hospitalized frequently and by the fifth decade of life, 48% of surviving patients have documented irreversible organ damage.[3] In Africa, where comprehensive medical care is less available, death in early childhood is usual.[2]

SCD in Saudi Arabia was first reported in the Eastern province in the 1960s.[4] This led to the initiation of multiple regional and national screening studies to determine the clinical characteristics and frequency of SCD genes in different regions of Saudi Arabia.[5-8] The epidemiology, molecular and clinical phenotypes of SCD in Saudi Arabia are reviewed and potential impact and future directions are identified in this review.

Molecular basis and origin of sickle cell disease in Saudi Arabia

It was initially thought that the sickle gene spreads by migration of a single mutation.[9] However, results of restriction fragment length polymorphism analysis on the beta-globin gene cluster indicate that the sickle gene mutation may have developed independently and spontaneously at least five times.[10,11] In Africa, the following four major sickle haplotypes are associated with a particular geographic region: 'Senegal' (Atlantic West Africa), 'Benin' (Central West Africa), 'Bantu' (also called 'CAR' for Central African Republic), and Cameroon.[11,12] The fifth major haplotype is the 'Arab-Indian' haplotype (also called the Asian or Saudi haplotype) is found in India and parts of Saudi Arabia.[10,11] This haplotype probably originated in the Indus Valley Harappa culture, and it was distributed to the Eastern part of the Arab peninsula through gene flow to the Eastern province of Saudi Arabia, Bahrain, Kuwait, and Oman.[11]

Although the molecular abnormality leading to the sickle gene is the same in all haplotypes, there is a wide variation in the clinical manifestations and severity of the associated disease. The clinical phe-

notype of SCD is said to be multigenic.[12] The sickle genotype (**Table 1**), beta globin haplotype, and other genes, unlinked to the beta globin locus, participate in the relevant pathological events that lead to modification of the phenotypic expression of the sickle gene.[12] Expression microarrays are being used to identify genes in several organs affected by the disease in man and sickle transgenic mice.[11] After these genes are located, polymorphisms can be searched for to identify genetic modifiers that will help define individual risk, allowing for rationale-based interventions before the onset of organ damage.[11] Among the genetic factors that have been associated with milder disease phenotype are alpha-thalassemia and high levels of fetal hemoglobin,[11] both are more commonly observed in SCD prevalent in the Eastern part of Saudi Arabia.[7,8] Environmental factors such as infections, nutrition, and socioeconomic status may also influence the course of the disease and the rate of survival. Therefore, each SCD patient has a unique genetic makeup and a unique environment that interact in different ways to modify the severity of the disease, and thereby make the clinical severity of SCD extremely variable.

The prevalence of sickle cell disease in Saudi Arabia

The prevalence of sickle-cell trait ranges between 10% and 40% across equatorial Africa and decreases to between 1% and 2% on the North African coast and less than 1% in South Africa.[13] This distribution reflects the fact that sickle-cell trait confers a survival advantage against malaria and that selection pressure due to malaria has resulted in high frequencies of the mutant gene, especially in the areas of high malarial transmission.[12] Although a single abnormal gene may protect against malaria, inheritance of two abnormal genes leads to SCD and confers no such protection, and malaria is one of the major causes of morbidity and death in children with SCD in Africa.[13,14]

Saudi Arabia has a population of 23.98 million.[15] Information about the prevalence of SCD in Saudi Arabia is patchy, but studies have reported that SCD is a relatively common genetic disorder in this part of the world.[4-8] The carrier status for SCD ranged from 2% to 27%, and up to 1.4% had SCD, in some areas.[4-8] These estimates of frequency are not based on newborn screening and probably underestimate the true frequency of SCD. In a nationwide survey of randomly collected blood samples, it was noted that the observed frequency of the sickle cell gene was significantly higher than the number expected using the Hardy-Weinburg principle which states that both allele and genotype frequencies in a population remain in equilibrium from generation to generation unless specific disturbing influences are introduced.[7] Autosomal recessive diseases are relatively common in this part of the world as consanguineous marriage rates exceed 50%.[16,17] This may explain the observed Hardy-Weinburg disequilibrium.[7]

The Saudi Premarital Screening Program estimated the prevalence of the sickle cell gene in the adult population at 4.2% for sickle-cell trait and 0.26% for SCD, with the highest prevalence noted in the Eastern province (approximately 17% for sickle-cell trait and 1.2% for SCD).[6] The disadvantage of premarital screening is that it is dependent on the incidence of disease at the time of marriage, the survival pattern of affected individuals up to the age of marriage, and disease severity. Therefore, such a screening program underestimates the true prevalence of SCD, particularly of the more

Table 1. Sickle cell disease genotypes.

SCD genotype	Definition	Clinical severity
HbSS disease or sickle cell anemia	Homozygote for the ßS globin gene	Usually severe or moderately severe phenotype
HbS/ßo thalassemia	Severe double heterozygote for HbS and ßo thalassemia	Usually indistinguishable from sickle cell anemia phenotypically
HbSC disease	Double heterozygosity for HbS and HbC	Intermediate clinical severity
HbS/ß+ thalassemia	Double heterozygosity for HbS and ß+ thalassemia	Mild to moderate severity, but variable in different ethnic groups
HbS/HPFH	HbS and hereditary persistence of fetal Hb	Very mild phenotype or symptom free as a result of high Hb F
HbS/HbE syndrome	Double heterozygosity for HbS and HbE	Very rare and generally very mild clinical course
Other rare combinations	HbS/HbD Los Angeles, HbS/HbO Arab, G-Philadelphia	Rare combinations with variable clinical course

severe type prevalent in the Western province. In a regional experience with newborn screening for SCD in the Eastern province over a 9-year period, the prevalence for sickle-cell trait was approximately 21% and for SCD was 2.6% (compared with 17% and 1.2%, respectively, from premarital screening).[6,18]

From the Premarital Screening Program, it was found that almost 90% of couples declared high-risk married each other despite being aware of the risk.[6] However, in an updated analysis reported in this issue of the *Annals* from the Premarital Screening Program the frequency of at-risk couples significantly decreased by approximately 60% with the frequency of voluntary cancellations of at-risk marriage proposals significantly increasing by 5-fold over 6 years.[19] This illustrates the significant success of the Saudi Premarital program in primary prevention of at-risk marriages to reduce the incidence of inherited disease. However, for a disease such as SCD, where early intervention is required to reduce the early morbidity and mortality associated with this disease, screening individuals earlier and integrating SCD with the neonatal screening program will add an interventional as well as a preventative role. This may be particularly true in the more severe 'Benin' haplotype prevalent in the Western province. There is evidence that neonatal screening for SCD, when linked to timely diagnostic testing, parental education, and comprehensive care, markedly reduces SCD morbidity and mortality.[20-22]

A number of economic studies have questioned the cost-effectiveness of screening for SCD in the United States and England and concluded that universal SCD screening at the national level met conventional criteria for cost-effectiveness.[23] Universal screening vs targeted screening has been shown to identify more infants with disease and prevent more deaths, and is cost effective in areas in which sickle trait occurs in 7 to 15 per 1000 births.[24,25] With an estimated prevalence of 4.2% of sickle-cell trait in Saudi Arabia,[6] the cost effectiveness of newborn screening is at least three fold greater.

From a recent statement by the World Health Organization, the most valid measure to study the impact of SCD on public health is under-5 years old mortality.[13] SCD contributes the equivalent of 5% of under-5 deaths in the African continent, more than 9% of such deaths in West Africa, and up to 16% of under-5 deaths in individual West African countries.[13] An increasing number of affected children currently survive five years of age but remain at risk of premature death, and 48% of patients surviving into adulthood have chronic organ dysfunction.[3]

Information on impact of SCD on under-five mortality in Saudi Arabia is absent and studies on mortality patterns are limited. However, hospital-based studies from the Eastern province show that 73% of deaths occur under the age of 30 years, with acute chest syndrome followed by infection as the major cause of deaths.[26]

Neonatal diagnosis allows provision of simple protective measures, including information for the parents, prophylaxis with penicillin, hydroxyurea, and transfusion therapy, all giving a better quality of life.[20-23] Neonatal diagnosis is useful only when there is appropriate counseling for the parents and adequate primary and follow-up care for those affected.

Clinical epidemiology of sickle cell disease in Saudi Arabia

The clinical manifestations of SCD are unpredictable and variable. Recently, two clinical phenotypes of SCD have been described.[27] In the hemolysis-associated phenotype, the characteristics are severe anemia, leg ulcers, and pulmonary hypertension. In the vaso-occlusion–related phenotype, the episodes of pain, acute chest syndrome, splenic infarction, stroke, and avascular necrosis of joints predominate. Endothelial dysfunction and vasculopathy also occur in SCD. Although its course is unpredictable, the disease is often associated with substantial morbidity, a decreased life span, and a poor quality of life. The risk of early death is highest among patients who have had severe complications, such as recurrent acute chest syndrome, renal failure, and pulmonary hypertension.[28,29] In contrast, many affected individuals have a good quality of life, and additional genetic and environmental factors may reduce the severity of the disease in some parts of the world.

The clinical phenotype of SCD in Saudi Arabia has two major forms (**Table 2**). Eastern patients have more deletional alpha thalassemia, higher total hemoglobin and fetal hemoglobin levels, and lower hemoglobin A2, mean cell volume, reticulocytes, and platelet counts.[30] Clinically, the disease carries a mild or benign phenotype. However, 'benign' is a relative term as patients with this type of disease have a different spectrum of disease with its acquired problems. For example, SCD patients from the Eastern province have a 27% risk of avascular necrosis of the femoral head compared with 8% to 12% in the African type.[30-32] Late persistent splenomegaly is reported in 50% to 80% of patients, resulting in a higher risk of splenic complications such as sequestration crisis, chronic hypersplenism, splenic infarction and abscess, trauma, and rupture, and 20% required splenectomy.[30,31] In the Western province, the frequency of splenomegaly is significantly less frequent.[30,31] Acute chest syndrome in SCD children less than 12 years of age occurs less

Table 2. Clinical phenotypes of SCD in Saudi Arabia: Eastern vs Western regions.

Variable	East	West
Haplotype	Arab-Indian	Benin
Coinheritance of alpha-thalassemia	More	Less
Clinical severity	Mild	Severe
Avascular necrosis of femoral head	Common	Uncommon
Late persistent splenomegaly	Common	Uncommon
Acute chest syndrome	Less	More
Recurrent acute chest syndrome	Less	More
Dactylitis	Less	More
Painful crisis	Late	Early
Stroke*	Less*	More*
Silent brain infarct*	Late*	Early*
Body build	Normal	Low
Priapism	Uncommon	Uncommon
Leg ulcers	Uncommon	Uncommon
Baseline hemoglobin level	Higher	Lower
Hemoglobin F level	Higher	Lower

*Studies are limited on stroke and silent brain infarcts but this is suggested as explained in the text.

commonly in the East compared with the West (7.7–13.4% vs 22.6%, respectively) and recurrence rate is significantly lower in patients from the Eastern province.[33] However, the difference in mortality rate from acute chest syndrome between both regions was not statistically significant.[26,30,33] Patients from the Eastern province had a more normal body build and greater subscapular skin fold.[29] Priapism and leg ulcers are relatively uncommon in both regions in Saudi Arabia.[8]

Dactylitis was significantly more common among patients from the Western province.[30] However, painful crisis affected equal proportions of patients in the two regions, although the onset was significantly later in age in Eastern patients.[30] This later onset suggests that SCD-related complications in the Eastern province may be delayed rather than totally ameliorated. This is also suggested from studies originating from Kuwait. In one study, complications rarely occurred before 5 years of age when the hemoglobin F level was approximately 30%, but with increasing age and decline in hemoglobin F level, clinical complications start occurring.[34] This is also illustrated in another article studying the prevalence of silent brain infarcts in SCD in Kuwait where the prevalence of silent brain infarcts before 17 years of age was 3.3%, whereas the prevalence was 20% at a median age of 31.8 years.[35,36] This is in contrast to reports from the Cooperative Study of SCD, in which the baseline prevalence of silent brain infarcts was 21.8% for children aged 6 to 19 years, with most infarcts occurring before 6 years of age in girls and with increasing prevalence until 10 years of age in boys.[37] This suggests that silent brain infarcts in the Arab-Indian haplotype occur with a similar prevalence to that reported in the African haplotype but in an older age group.

Overt stroke occurs in 7% to 13% of children with SCD and can lead to motor disability, neuropsychological impairment, and death.[38] Studies on the incidence of stroke in SCD in Saudi Arabia are limited. From a hospital-based study of SCD from the Western part of Saudi Arabia, the incidence of overt stroke in children up to the age of 12 years was 9.4%.[39] Information on the incidence of stroke in children with SCD from the Eastern part of Saudi Arabia is lacking but may be lower.[40] However, patients with SCD in the Eastern province who are homozygous for the G6PD Mediterranean S188F mutation were at a significantly higher risk of developing stroke.[41] This underscores the effect of genetic modifiers even on a 'benign' haplotype.

Therefore, the clinical phenotype of SCD in Saudi Arabia is different. The disease in the Western province is more severe, consistent with the Benin haplotype. Although the disease in the Eastern province has many mild features, splenic complications and bone pathology are more common; in addition, complications such as pain crisis and vasculopathy occur at a later age. This highlights the need for long-term comprehensive care with special attention and timely screening of SCD-related complications in each region. Further long-term morbidity and mortality studies at a national level are needed to study the morbidity and mortality patterns and the effect of standardized comprehensive and supportive care programs.

Future directions and conclusion

SCD is prevalent in Saudi Arabia and is probably underestimated. The variable genetic origin and variable clinical phenotype of SCD between the East and West parts of Saudi Arabia make it possible to further pursue research on genetic, clinical, and environmental modifiers of SCD. There is a need for systematic, prospective studies that document the prevalence, molecular and clinical epidemiology of SCD in different areas of Saudi Arabia to help predict disease severity, risk stratify patients to receive early intensive care or continued symptomatic care,

and describe the problems currently faced by patients affected with SCD in Saudi Arabia.

Initial research efforts should probably focus on newborn screening to study the true prevalence and impact of SCD in Saudi Arabia, transfusion practice, and the effect of multigenic and environmental factors on morbidity and mortality patterns. Particular emphasis should be given to the factors that are already suspected to play a major role in SCD-associated morbidity and mortality, such as infection, acute chest syndrome, and stroke, for which potential prophylactic and treatment options already exist.[20-22]

Taking forward a joint care-and-research agenda will require the strengthening of institutions that have the resources to act as national and regional centers of excellence for SCD research, treatment, and training. Such strengthening is essential if the capacity to provide SCD care at all levels of the health service is to be improved. Unfortunately, current expenditure on both research on, and the clinical care of, SCD patients is negligible, and there is a need for ministries of health, medical institutions, research organizations, and international agencies to work together to develop a clear strategy to achieve this goal.[42]

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