



Sickle Cell Anemia

Alternative Names

SCA
Sickle Cell Disease
SCD
Hemoglobin SS Disease

WHO International Classification of Diseases

Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

OMIM Number

603903

Mode of Inheritance

Autosomal Recessive

Gene Map Locus

11p15.5

Description

Sickle cell disease refers to a collection of genetic blood disorders characterized by a hemoglobin variant called (HbS). Individuals who are affected with sickle cell anemia have two copies of this beta globin variant, and the primary hemoglobin present in their red blood cells is (HbS). This disease is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy. Sickle cell anemia is an inherited autosomal recessive disorder characterized primarily by chronic anemia and periodic episodes of pain. The disorder produces abnormal hemoglobin, which causes the red blood cells to sickle or become crescent-shaped. These sickle shaped RBCs are much less deformable, and therefore obstruct microcirculation, and cause tissue infarction. This can result in hand-foot syndrome, fatigue, paleness, and shortness of breath, pain that occurs unpredictably in any body organ or joint,

eye problems, yellowing of skin and eyes, delayed growth and puberty in children and often a slight build in adults. Other complications include infections, stroke, and acute chest pain.

Individuals who possess one copy of the normal beta globin gene (HbA) and one copy of the sickle variant (HbS) are referred to as having sickle cell trait, but these individuals do not express symptoms of sickle cell disease. Individuals affected with other types of sickle cell diseases are heterozygotes, with HbS and other beta-globin gene variants, like HbC and Hb beta-thalassemia. The prevalence of this disease in Africa, the Mediterranean and the Middle East is attributed to the increased protection to malaria infection in heterozygous carriers. Treatments, such as penicillin prophylaxis, have been developed that can significantly reduce the morbidity and mortality of sickle cell disease.

Molecular Genetics

Sickle cell anemia results from an A to T transversion at the sixth codon of the hemoglobin beta globin gene on chromosome 11p15.5. The mutation of a single DNA base leads to the substitution of a valine for a glutamic acid in the beta globin polypeptide of sickle hemoglobin (HbS). Deoxygenation of the heme moiety of HbS leads to hydrophobic interactions between adjacent HbS molecules, which then aggregate into larger polymers, distorting the red blood cell (RBC) into the characteristic sickle shape. At least five different haplotypes are linked to the sickle gene, each of which can be identified based on mutation analysis in the promoter sequences of the G-gamma and A-gamma globin genes. These haplotypes are named following the geographical locations where they most occur. Namely, the Arabia-Indian haplotype is characterized by significantly higher levels of fetal hemoglobin (HbF) levels and a milder



course of the disease. In contrast, patients with the African haplotypes, Bantu and Benin, express relatively lower levels of HbF with severe clinical presentations.

Epidemiology in the Arab World

Algeria

Dahmane-Arbane et al. (1987) report a case of Hb Boumerdes, an alpha chain variant alpha 2(37) (C2) Pro----Arg beta 2, in an Algerian family. The propositus was also homozygous for the sickle cell gene. The abnormal hybrid hemoglobin had an electrophoretic mobility on cellulose acetate pH 8.7 electrophoresis between those of Hb S and Hb A2. Its expression was about 16%. The propositus' sickle cell phenotype was benign.

Bahrain

Buhazza et al. (1985) evaluated the hematological findings of 50 Bahraini patients with sickle cell disease. Family studies were done on both parents of 15 families and on seven other single parents. A control group of 21 newborns and 20 normal adults was also examined. Methods of analysis included electrophoresis, alkali denaturation method, and column chromatography. Hb F level of the 50 patients showed a range from normal to 54.2% which was lower than those encountered in surrounding countries. Of the 37 parents, 8.1% were homozygous for the disease, 8.1% were doubtfully beta-thalassemia heterozygotes, and 83.8% were Hb S heterozygotes. Buhazza et al. (1985) found that most of the parents were consanguineous. Three subjects (15%) in the control group were identified to be heterozygotes for the sickle gene, which indicates a high heterozygote frequency for the disease among Bahrainis.

El-Shafei et al. (1988) studied the complications during pregnancy of 100 consecutive unselected mothers. Thirty five of the mothers were SS, and 65 were AS. The results were compared to a control group of 200 women. The incidence of vaso-occlusive crisis was significant in mothers with sickle cell disease related to low socio-economic groups. Also, the high level of HbF had no beneficial effect during the crisis episodes in sickle mothers.

Rasromani et al. (1990a) studied the prevalence of cholelithiasis in sickle cell disease and the relationship of its frequency to age and hematological parameters (hemoglobin and hemoglobin F values, microcytosis and reticulocyte count). Sixty-five patients with

sickle cell anemia attending Salmaniya Medical Center in Bahrain were included in the study. The diagnosis of sickle cell anemia was established by a sickling test, hemoglobin electrophoresis, and family studies. Ultrasonography was performed to visualize the gallbladder. In 22 (34%) of the patients, abdominal ultrasound was abnormal; 19 of these (86.5 %) had multiple gallstones, while two had biliary sludge, and one had a solitary gallstone. Rasromani et al. (1990a) did not find any significant relationship between the frequency of cholelithiasis and age or hematological parameters. Furthermore, Rasromani et al. (1990b) interviewed 50 sickle cell patients in Bahrain for history of priapism. Although priapism is a common complication in sickle cell patients (Black Americans-50%, Jamaicans-42%), Rasromani et al. (1990b) reported only one of the 50 patients to have suffered from it. The Bahraini patients were shown to have high HbF and low MCV values. The high HbF and microcytosis may play a protective role against the corpora cavernosa venous obstruction and priapism.

Al Arrayed and Haites (1995) examined sickle cell disease among Bahrainis in four separate studies. In the first study, Al Arrayed and Haites (1995) observed the prevalence of SCD in the hospital population of Bahrain over six years. The study included 5,503 neonates and 50,695 non-neonates. Of the neonatal samples, 18.1% showed sickle cell trait, and 2.1% had sickle cell disease. The frequency of sickle cell disease in non-neonatal patients was found to be 10.44%, and 84% of the sickle cell disease patients had HbF. The second study examined the nature of sickle cell disease by sending a questionnaire to 100 school children with sickle cell disease. Al Arrayed and Haites (1995) found that the most common factors precipitating crisis in sickle cell disease children are cold, fever, and physical activity. Most of the sickle cell disease school children had pain in hands, limbs, abdomen, knee, and back. The mortality rate was low. Since only 10% of school patients had experienced the death of family members, due to sickle cell disease. This was attributed to their high level of HbF, and high prevalence of alpha-thalassemia gene. Al Arrayed and Haites (1995) also determined the hematological characteristics of Bahraini sickle cell disease patients. Most of the patients had low hemoglobin levels, low HCT, low MCH, and low MCV (microcytosis) levels. The later was thought to be due to the co-existence of alpha-thalassemia gene. Al Arrayed and Haites (1995) did the fourth study to detect the Beta-S gene haplotypes among Bahraini populations.



PCR and restriction digestion were the main procedures for the study. Of 59 individuals from 19 families, 59% were carriers. The Asian haplotype was presented in all the 19 families, with a frequency of 90%. The second most common haplotype was S2 haplotype (5%) followed by the S1 African haplotype (2.5%).

Kuwait

Adekile et al. (1994) characterized the beta-S chromosomes among Kuwaiti Arabs. PCR, hybridization and DNA sequencing techniques were used to analyze 18 beta-S chromosomes. Haplotype 31 (Saudi Arabia/Indian) was carried by 77.8% of the chromosomes and the Benin haplotype (19) occurred in 16.7% of the chromosomes.

Oman

White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of sickle cell disease in Oman to be 3.8%.

In a study on the hemoglobinopathies in the United Arab Emirates, Baysal (2001) examined the HbS gene in 50 Omani patients with sickle cell disease. Haplotype homozygosity was prevalent in the population (80%). The Benin haplotype was the most common in the population (34%), followed by the Bantu haplotype (24%), and the Saudi Arabian/Indian haplotype (22%); suggestive of the East African influence on the Arabian Peninsula and on Oman in particular.

In two members of an Arabian family from Oman, Ramachandran et al. (1992) discovered a leu-to-val replacement at position beta-32 by reversed phase high performance liquid chromatography. In one person, it occurred with Hb S and in the other with Hb A.

Nagel et al. (1998) studied a pedigree of heterozygous carriers of Hb S (Oman) that segregated into 2 types of patients: those expressing about 20% Hb S (Oman) and concomitant -alpha/alpha-thalassemia and those with about 14% of Hb S (Oman) and concomitant -alpha/-alpha-thalassemia. The higher expressors of Hb S (Oman) had a sickle cell anemia clinical syndrome of moderate intensity, whereas the lower expressors had no clinical syndrome and were comparable to the solitary case first described in Oman. In addition, the higher expressors exhibited a unique form of irreversibly sickled cell reminiscent of a 'yarn and knitting needle' shape, in addition to folded and target cells. Purified Hb S (Oman) has a C(SAT) (solubility

of the deoxy polymer) of 11 g/dL, much lower than Hb S alone (17.8 g/dL). Another double mutant, Hb S (Antilles) (141900.0244), has a similarly low C(SAT) and much higher expression (40 to 50%) in the trait form, but has a phenotype that is similar in intensity to the trait form of Hb S (Oman). Nagel et al. (1998) concluded that the pathology of heterozygous S (Oman) is the product of recipient properties of the classic mutation which are enhanced by the second mutation at beta-121. In addition, the syndrome is further enhanced by a hemolytic anemia induced by the beta-121 mutation. They speculated that the hemolytic anemia results from the abnormal association of the highly positively charged Hb S (Oman) (3 charges different from normal hemoglobin) with the RBC membrane.

Palestine

Fathalla (1986) reported a case of sickle-thalassemia with the hand-foot syndrome in a 12-year-old Palestinian boy. The patient, previously diagnosed with sickle-thalassemia at the age of 3 years, was admitted to the hospital because of severe pain in both hands for two days after an exposure to cold weather. Clinical investigations showed typical features of chronic hemolytic anemia, the spleen enlarged to about 4 cm below the left costal margin and the liver about 3 cm below the right margin. The patient's upper extremities were normal except for diffuse swollen small joints of both hands with shiny warm skin. Radiographic examinations of both hands revealed wide medullary cavities and thinning of the cortex of the metacarpal bones with diffuse soft tissue swelling. Fathalla (1986) noted that this case seemed to be an unusual presentation of hand-foot syndrome, since to his knowledge a similar case has not been reported in the literature with the onset of symptoms after exposure to cold weather. Fathalla (1986) also suggested that avoidance of cold should be considered as an important factor in preventing sickle cell crisis.

Saudi Arabia

Wood et al. (1980) studied fetal hemoglobin (HbF) synthesis in 22 cases of sickle cell anemia from Saudi Arabia and compared with an equal number of cases of African origin. Among the Saudi Arabs gamma chain synthesis ranged from 4.0% to 19.9% of the total non-alpha chain synthesis (mean 8.1%) while the corresponding range for the Negro cases was < 0.3% to 4.6% (mean 1.7%). In both groups the peripheral blood HbF level was on average 3-4 times higher than the proportion synthesized, indicating that the selective survival of HbF containing cells (F cells) was an important



factor in determining the final H F levels. Wood et al. (1980) realized that a high proportion of the cases in both groups were carriers of alpha thalassemia in addition to sickle cell, but did not observe any effect of alpha thalassemia on HbF production.

Kulozik et al. (1986) found that the sickle gene in Saudi Arabia and on the west and east coasts of India exists in a haplotype not found in Africa. They concluded that the data are most consistent with an independent Asian origin of the sickle cell mutation. The distribution of the Asian beta-S-haplotype corresponded to the reported geographic distribution of a mild clinical phenotype of homozygous SS disease.

Patients from the eastern province of Saudi Arabia who have sickle cell anemia have high circulating levels of fetal hemoglobin, 17% H F on the average, and, as a consequence, have a mild form of the disease. Miller et al. (1987) found a single-base cytosine-to-thymidine substitution at the 158 bp 5-prime to the cap (preinitiation) site of the G-gamma-globin gene of the high-hemoglobin-F chromosome. The substitution was present in nearly 100% of patients with sickle cell disease or trait and in 22% of normal Saudis. Homozygosity for this mutation had no demonstrable effect on hemoglobin F production in the normal Saudi population.

Abbag (1997) analyzed febrile illnesses in young patients with sickle cell disease in the Southwest region of Saudi Arabia. Data was collected on 269 admissions of 94 young patients, 66 boys and 28 girls in Southwest Saudi Arabia. Blood culture was performed in patients with temperatures over 38 degrees C. Of the 207 admissions due to SCD crisis, 53.6% admissions had associated fever, of which, 71.2% were associated with fever without obvious infection. The infections found in patients with temperature over 38.5 degrees C, were upper respiratory tract infection (18.8%), pneumonia (10.4%), septicemia (6.3%), osteomyelitis (5.2%), urinary tract infection (4.2%), gastroenteritis (3.1%), malaria, septic arthritis, and cervical lymphadenopathy (one patient each). Sickle cell disease patients are particularly susceptible to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Salmonella* species, and other Gram negative bacteria. However, the study of Abbag (1997) identified only one patient with a serious infection of *Streptococcus pneumoniae*, pointing to the rarity of this infection in sickle cell patients in Southwest Saudi Arabia. Half of the cases of septicemia and probably three of the five cases

of osteomyelitis were due to *Salmonella typhi* infection, suggesting a possible choice of antibiotics to effectively combat febrile infections in sickle cell patients

Zaki and Al Husain (1999) described a boy who had the karyotype [46, XY, del(3) (q21q25.3)], which suggested the presence of the deletion syndrome. The parents were first cousins with normal karyotypes. The boy was heterozygous for the sickle cell gene.

Sudan

Prehu et al. (2002) described a heterozygous hemoglobin variant that combined the change of Hb O-Arab and Hb Hamilton on the same beta-globin allele. The other allele carried the Hb S mutation. The patient was a child of Chad-Sudanese descent, suffering from a sickle cell syndrome. Compared to the classic description of the Hb S/Hb O-Arab association, the additional Hb Hamilton mutation did not seem to modify the clinical presentation.

United Arab Emirates

White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of sickle cell disease in the United Arab Emirates to be 1.9%.

Awaad and Bayoumi (1993) studied the severity of sickle cell disease (SCD) in adult Bedouins in Al-Ain Hospital. The parameters used to gauge severity of SCD included frequency of admissions crisis, blood transfusion requirements, and complications. Methods used included Coulter S7, agarose gel electrophoresis, column chromatography, and alkali denaturation. There were two groups: homozygous SCD and heterozygous for SCD and beta thalassemia. The homozygous SCD patients showed normal MCV, MCH and HbA2 levels, while the SCD/beta-thalassemia patients had low MCV, MCH and high HbA2. The HbF level was elevated in all patients, and that did not seem to relate to the clinical severity of the disease. There was no noticeable difference in the severity of the disease between homozygous SCD and SCD/beta-thalassemia, which ranged from mild to moderate.

El-Kalla and Baysal (1998) examined 46 UAE nationals for their genotype-phenotype correlation of sickle cell disease. Disease severity was scored according to clinical manifestations. Methods for analysis included Coulter counting, Isoelectric focusing, column chromatography, alkali denaturation assay, hybridization, DNA sequencing, ARMS, and mutation analysis. El-Kalla and Baysal (1998)



identified three beta-S haplotypes in the UAE population: the Arabian Indian haplotype 31, the Bantu haplotype 20, and the Benin haplotype 19. Haplotype 31 was the most common and was associated with elevated mean HbF levels, as compared to the other two haplotypes. This resulted in less severe clinical symptoms, and a majority of the patients with this haplotype did not require blood transfusion at all. Most of the sickle cell patients had concomitant alpha-thalassemia, which in turn reduced the severity of their disease. El-Kalla and Baysal (1998) identified eight different beta-thalassemia mutations in heterozygous condition with the HbS allele. Seven of these eight mutations were beta-zero and, their coexistence with the sickle gene, manifested severe clinical symptoms. El-Kalla and Baysal (1998) examined three UAE families with Hb SD; one family with haplotype 20 and one with haplotype 19. All of them suffered from severe forms of the disease and required repeated blood transfusions. A 5-year-old Hb SD UAE national boy with haplotype 19 (HbF level 28%, silent alpha-thalassemia) was transfusion dependent and also had a splenic sequestration crisis at the age of 9 months. Another 6-year-old Hb SD girl, also from UAE, with haplotype 20 (HbF level 5%, silent alpha-thalassemia) had a cerebrovascular crisis that caused brain infarction. The study of El-Kalla and Baysal (1998) showed that the sickle cell disease is genetically complex and multifactorial, and that epistatic factors influence the severity of the disease to a large extent.

In a study on the hemoglobinopathies in the United Arab Emirates, Baysal (2001) examined the HbS gene in UAE nationals with sickle cell disease. The Saudi Arabian/Indian haplotype was the most prevalent in the population (68%) followed by the Bantu haplotype (8%), signifying the presence of an African influence.

Baysal (2005) examined beta-globin alleles in 313 beta-thalassemia patients nationals of the UAE using column chromatography, isoelectric focusing, restriction enzyme analysis, beta strip hybridization, PCR, and DNA sequencing. Of the total chromosomes analyzed, 21.9% carried the HbS allele. Additionally, of the 101 heterozygous individuals examined by Baysal (2005), 16% were compound heterozygotes for HbS, making it the second most common beta globin gene defect in the UAE.

[See also: Palestine > Fathalla, 1986 and Oman > Baysal, 2001].

Yemen

White et al. (1986) analyzed 5000 subjects from three major Peninsular Arab States and determined the frequency of sickle cell disease in Yemen to be 0.95%.

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