To know about Sickle cell anemia disease

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Abstract

Mutations in HBB, which encodes the haemoglobin component, are the basis for the genetic diseases known as sickle cell disease (SCD). The bulk of cases are thought to occur in sub-Saharan Africa, where the frequency is thought to be between 300,000 and 400,000 neonates annually. Mutant sickle globin subunit-containing hemoglobin molecules have the ability to polymerize, and erythrocytes that mostly contain sickled hemoglobin polymers are susceptible to hemolysis. Vaso-occlusion and immune system activation are additional pathophysiological pathways that contribute to the SCD phenotype. An astounding phenotypic complexity distinguishes SCD. Chronic problems, such as chronic renal disease, can harm all organs. Common acute complications include acute pain episodes, acute chest syndrome, and stroke. Blood transfusions, hydroxycarbamide, and haematopoietic stem cell transplantation can all lessen the severity of the illness. Universal newborn screening programs have been adopted in several countries, but they are hard in low-income, high-burden settings. Early diagnosis is essential to enhance survival.

I. Introduction

A set of genetic disorders characterized by mutations in the gene encoding the haemoglobin subunit (HBB) and characterized by sickle cell anemia (SCA), HbSC, and HbS-thalassaemia are together referred to as sickle cell disease (SCD) (Fig. 1). Each globin component is connected to the cofactor haem, which can transport an oxygen molecule, and together they make up the tetrameric protein known as hemoglobin (Hb). Red blood cells, including reticulocytes (immature red blood cells) and erythrocytes (mature red blood cells), express hemoglobin (Hb). Different varieties of Hb are generally expressed at different times of life, including embryonic, fetal, and adult. Several genes encode distinct types of globin proteins, and their varied tetrameric combinations produce multiple types of Hb. The most prevalent form of adult hemoglobin, known as hemoglobin A (HbA), has two -globin subunits (produced by the duplicated HBA1 and HBA2 genes) and two -globin subunits. The sickle Hb (HbS) allele is created by a single nucleotide change in HBB; the mutant protein produced by the S allele is the sickle -globin subunit and has an amino acid substitution. The erythrocytes can take on a crescent or sickled form as a result of the polymerization of Hb tetramers that contain two of these mutant sickle -globin subunits (i.e., HbS) during conditions of deoxygenation (i.e., when the Hb is not linked to oxygen). Although less effectively than HbS, Hb tetramers with one sickle -globin component can also polymerize. Sickle erythrocytes can cause SCD's characteristic recurring vaso-occlusive episodes.

SCD is inherited as an autosomal codominant trait; those who are homozygous for the S allele have SCA, whereas those who are heterozygous for the S allele possess the sickle cell trait (HbAS) but do not have

SCD. The most typical form of SCD, SCA, is a chronic condition marked by widespread organ damage, unpredictable pain episodes, and persistent hemolytic anemia. Both the life expectancy and the clinical severity of SCA are highly variable. High levels of fetal Hb (HbF; the heterodimeric mixture of two -globin proteins and two -globin proteins (encoded by HBG1 and HBG2)) and the co-inheritance of -thalassaemia (which is caused by mutations in HBA1 and HBA2) are consistently linked to milder SCD phenotypes, according to genetic and genome-wide association studies. However, only a small portion of the observed phenotypic heterogeneity is explained by these two biomarkers.

A rapidly growing corpus of knowledge has contributed to a better understanding of SCD since the 1980s, especially in high-income nations. In the US, funding for research has skyrocketed, awareness and education campaigns have expanded, counseling campaigns have improved, and universal newborn screening campaigns now guarantee early detection and intervention. A cadre of knowledgeable health professionals working in this field is the result of specific research and training programs, which also improved patient management, prevented problems, and increased life expectancy.

II. Epidemiology

Particularly in regions with high prevalence, there is not a lot of knowledge on the natural history of SCD, which is important for SCD prevention and control. The two main sources of data are the Cooperative Study of Sickle Cell Disease (CSSCD; 1978-1998) in the United States, which collected information on growth and development, disease complications, clinical studies, and epidemiology on more than 3,000 SCD patients, and the Jamaican Cohort Study of Sickle Cell Disease, which was started in 1973 and followed up all SCD patients found among 100,000 consecutive deliveries in Kingston, Jamaica. Since the CSSCD was terminated, a few single-institution ongoing registries, screening cohorts of clinical trials, and administrative health data sets can be used to determine the ongoing natural history of SCD in the United States.

Numerous cohort studies in high- and middle-income nations have shown that the clinical course of SCD in both children and adults has significantly changed since the 1970s. Children with SCA have been found to live as long as healthy children in the United States and the United Kingdom. A median longevity of 67 years has been reported for patients with SCD at one London hospital; nevertheless, survival is still significantly lower than that of the overall population of London. Adults with SCD in high-income nations can now be expected to live well into their sixties. The transition from pediatric to adult patterns of lifestyle and medical care delivery is becoming more crucial as the juvenile mortality rate for SCD has decreased. For instance, the number of adult haematologists in the United States with specialized training in SCD is dwindling; therefore adults with SCD are treated by primary care physicians or by haematologists-oncologists with a limited amount of SCD experience. There is a paucity of information on SCD patients' survival in sub-Saharan Africa and India. According to data from African studies, 50–90% of children under the age of five die from SCA.

III. Prevalence and incidence

According to estimates, there were 230,000 SCA births in sub-Saharan Africa in 2010. This represents 75% of all SCA births worldwide. In addition, HbSC illness, the second most typical form of SCD16, is most prevalent in West Africa. These figures are expected to rise during the next 40 years, especially in sub-Saharan Africa17. According to estimates from 2010, sub-Saharan Africa had more than 3.5 million

newborn newborns with HbAS who could benefit from a strong defense against deadly P. falciparum malaria and its accompanying mortality. No African nation has yet launched a countrywide SCD1screening program. Estimating the frequency, incidence, and impact of disease remains difficult, even in nations with universal screening programs that have been in existence for more than ten years (such as the United Kingdom). During 1.1 million newborns in the United States had the HbAS genotype, and 40,000 confirmed instances of SCD have been found in 76 million newborns during the past 20 years. As a result, SCD affected 1 in every 1,941 neonates, and 1 in every 67 individuals had the heterozygous S mutation.

Because of the ethnic diversity of the Brazilian population, the frequency of SCD in newborn neonates varies greatly between Brazilian states. One in 650 newborns in the state of Bahia, one in one hundred in the state of Rio de Janeiro, and one in thirteen thousand five hundred in the state of Santa Catarina were checked for SCD in 2014. Over 60,000 infants were heterozygous for the S allele and 1,071 newborns nationwide developed SCD in 2016 (F.F.C., unpublished observations). In the entire nation, 30,000 people are thought to have SCD. Depending on the area, the prevalence of the S allele in Brazil ranges from 1.2% to 10.9%, whereas the prevalence of the C allele is estimated to be between 0.15% and 7.4%25-30. Currently, there is no reliable estimate of the total number of people of all ages who are affected by SCA worldwide due to the dearth of epidemiological data, particularly mortality statistics, in regions with high prevalence.

IV. Diagnosis, screening and prevention

The objectives and procedures for diagnosing SCD change depending on the patient's age. Preconception, prenatal, neonatal, and post-neonatal testing periods generally overlap. Preconception testing is intended to find asymptomatic potential parents who might pass down SCD to their offspring. Preconception testing uses standard, fundamental protein science laboratory procedures including Hb electrophoresis, high-performance liquid chromatography (HPLC), and isoelectric focusing100 that allow separation of Hb species based on their protein structures. Couples who tested positive at preconception screening are given the option of prenatal diagnosis, an early pregnancy procedure that is generally safe but invasive. It needs fetal DNA samples from an examination of the chorionic villus at 9 weeks' gestation. Techniques for non-invasive prenatal diagnosis are being developed, although they are still in the research stage. By as early as 4 weeks of gestation, these novel methods can identify fetal DNA in the maternal circulation. If pre-implantation genetic diagnosis is available, some couples who test positive during preconception screening may choose to undergo in vitro fertilization in order to genetically identify at-risk embryos prior to embryo transfer.

Newborn screening

Before any symptoms appear, newborns are screened for SCD at birth using Hb protein analysis techniques. There are two different kinds of newborn screening programs that have been used: targeted screening, which targets infants with high-risk parents, and universal screening. In general, universal screening is more economical, finds more sick newborns, and prevents more fatalities. At around 21 months of age, SCD is initially diagnosed in regions lacking neonatal screening programs. A deadly infection or an acute splenic sequestration crisis is the typical initial presentations for many people with SCD. The mortality rate in the first five years of life is reduced from 25% to 3% by early diagnosis,

penicillin prophylaxis, and family education. In low-income nations, similar encouraging outcomes are observed.

Post-neonatal testing

The need for post-neonatal SCD testing is determined by a number of variables that affect how well the general public is informed about their SCD status. These elements include availability to newborn screening findings for older patients, immigration of at-risk patients who have not been examined, and regional success of neonatal screening programs. Despite the fact that HbAS is a benign condition and not a disease, it increases the chance of several rarely occurring significant complications. Therefore, understanding one's own HbAS status is crucial for family planning and the prevention of rare but critical problems.

Newborn screening programs can also detect HbAS, but this is not their main goal, thus many of them don't give this information or provide any related counseling. Screening should be conducted on those who intend to become parents to identify heterozygous genes that may be crucial for genetic counseling. Making educated judgments about preconception counseling and prenatal diagnosis is made possible by HbAS screening.

For people with HbAS, regular exercise training does not raise the risk of mortality. However, there is a worry that vigorous, protracted physical activity increases the risk of rhabdomyolysis (rapid skeletal muscular breakdown) and sudden mortality; this risk can be reduced by appropriate training. These findings have led to the voluntary or required screening of athletes for HbASin some areas. There are a few unique and uncommon HbAS problems that call for testing. These include hyphema (blood in the eye's anterior chamber), haematuria (blood in the urine), and renal medullary carcinoma, a rare cancer. HbAS may be a risk factor for pulmonary embolism and chronic renal disease.

V. Management

SCD is a multisystem, complex illness with both acute and chronic consequences. In high-income countries, the life expectancy of people with SCA has significantly increased due to advances in general medical care, early diagnosis, and comprehensive treatment because practically all patients live past the age of 18. The quality of life for those with SCD frequently declines during adulthood, life expectancy is still reduced by about 30 years, and the social and psychological effects of SCD on affected people and their families are still underappreciated. Despite the best medical care available, these issues still exist. Additionally, the majority of these advancements have not reached low-income nations.

Therapies

Hydroxycarbamide

Ribonucleotide reductase inhibitor hydroxycarbamide, also known as hydroxyurea in some countries, increases HbF expression (in the majority of people with SCA) and lowers leukocyte count, among other physiological consequences. Both the US FDA and the European Medicines Agency (EMA) approved it for the treatment of SCD in 1998 and 2007, respectively. The medication has an excellent safety profile and significantly lowers the frequency of SCA vaso-occlusive crises, hospitalizations, and mortality in high-income countries (studies in low-resource countries are still ongoing). Nevertheless, some patients

do not respond favorably, typically due to restrictions in adherence to treatment but possibly occasionally for pharmacogenomic reasons. Inadequate health care infrastructure in both high- and low-resource nations, as well as erroneous beliefs about hydroxycarbamide's carcinogenicity, teratogenicity, and reduced fertility, which have not yet been problems in follow-up studies.

Erythrocyte transfusion-

This treatment reduces the amount of sickle erythrocytes in the blood, which increases microvascular flow and is linked to less endothelial damage and inflammatory damage. Chronic transfusion therapy can lessen and prevent stroke and vaso-occlusive crises; however, several potential side effects, including iron overload, alloimmunization (an immune response to foreign antigens present in the donor's blood), and hemolytic transfusion reactions limit its potential benefits. Chronic transfusion therapy is typically prescribed in high-resource countries to the roughly 10% of patients with SCA at high risk of stroke. The negative consequences of iron overload have decreased since oral iron-chelating medications became available in 2005. There are significant hazards of transmission of blood-borne illnesses such hepatitis B, hepatitis C, HIV infection, West Nile virus infection, and others in nations where testing of blood products for infectious agents is inadequate. The safety of this treatment is enhanced by iron-chelation therapy recommendations and transfusion protocols with extended erythrocyte matching that includes the erythrocyte antigens Kell, C, E, and Jkb. To lessen alloimmunization, systematic genotyping of the patient's blood groups has been suggested.

Haematopoietic stem cell transplantation-

In SCA, hemopoietic stem cell transplantation is curative and need to be taken into consideration by symptomatic individuals who have a family donor who matches their HLA. Nearly 2,000 SCA patients are thought to have received an allogeneic hematopoietic stem cell transplant globally; US and European studies show that the survival rate is above 90%. The average rate of acute and chronic graft-versus-host disease, which is typically lower with newer approaches158, has been 14% in pooled registry data, and the percentage of graft failure has been 2%. The preliminary outcomes of experimental reduced-intensity conditioning regimens (pretransplant chemotherapy to destroy or suppress the recipient's bone marrow) are highly promising. However, the majority of patients lack a related donor who can match their HLA. Haploidentical donors, who share 50% of the recipient's HLA antigens, and unrelated HLA-matched donors are two types of extended donor pools that have been used experimentally to raise the likelihood of cure but also substantially increase mortality and graft rejection rates. It is possible to treat SCA with a haematopoietic stem cell transplant from the bone marrow of a healthy HLA-matched donor, but only high-income nations offer this treatment.

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