Sickle cell disease

Sickle cell disease (**SCD**) is a group of blood disorders typically inherited from a person's parents.[2] The most common type is known as **sickle cell anaemia** (**SCA**).[2] It results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells.[2] This leads to a rigid, sickle-like shape under certain circumstances.[2] Problems in sickle cell disease typically begin around 5 to 6 months of age.[1] A number of health problems may develop, such as attacks of pain ("sickle cell crisis"), anemia, swelling in the hands and feet, bacterial infections and stroke.[1] Long-term pain may develop as people get older.[2] The average life expectancy in the developed world is 40 to 60 years.[2]

Sickle cell disease occurs when a person inherits two abnormal copies of the haemoglobin gene, one from each parent.[3] This gene occurs in chromosome 11.[9] Several subtypes exist, depending on the exact mutation in each haemoglobin gene.[2] An attack can be set off by temperature changes, stress, dehydration, and high altitude.[1] A person with a single abnormal copy does not usually have symptoms and is said to have sickle cell trait.[3] Such people are also referred to as carriers.[5] Diagnosis is by a blood test, and some countries test all babies at birth for the disease.[4] Diagnosis is also possible during pregnancy.[4]

The care of people with sickle cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication.[5][6] Other measures may include blood transfusion and the medication hydroxycarbamide (hydroxyurea).[6] A small percentage of people can be cured by a transplant of bone marrow cells.[2]

As of 2015, about 4.4 million people have sickle cell disease, while an additional 43 million have sickle cell trait.[7][10] About 80% of sickle cell disease cases are believed to occur in Sub-Saharan Africa.[11] It also occurs relatively frequently in parts of India, the Arabian Peninsula, and among people of African

Sickle cell disease	
Other names	Sickle cell disorder

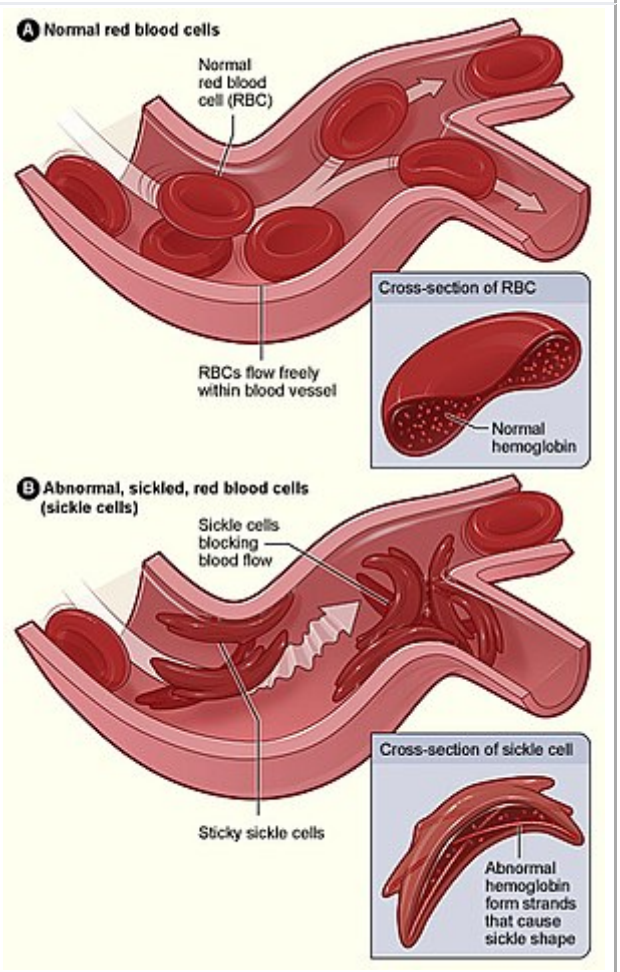


Figure (A) shows normal red blood cells flowing freely through veins. The inset shows a cross section of a normal red blood cell with normal haemoglobin. Figure (B) shows abnormal, sickled red blood cells sticking at the branching point in a vein. The inset image shows a cross-section of a sickle cell with long polymerized sickle haemoglobin (HbS) strands stretching and distorting the cell shape to look like a crescent.

Specialty	Hematology
Symptoms	Attacks of pain, anemia, swelling in the hands and feet, bacterial infections, stroke[1]
Complications	Chronic pain, stroke, aseptic

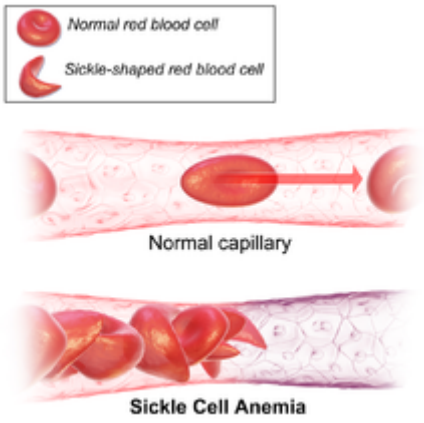
origin living in other parts of the world.[12] In 2015, it resulted in about 114,800 deaths.[8] The condition was first described in the medical literature by American physician James B. Herrick in 1910.[13][14] In 1949, its genetic transmission was determined by E. A. Beet and J. V. Neel.[14] In 1954, the protective effect against malaria of sickle cell trait was described.[14]

	bone necrosis, gallstones, leg ulcers, priapism, pulmonary hypertension, vision problems, kidney problems[2]
Usual onset	5–6 months of age[1]
Causes	Genetic[3]
Diagnostic method	Blood test[4]
Treatment	Vaccination, antibiotics, high fluid intake, folic acid supplementation. pain medication, blood transfusions[5][6]
Prognosis	Life expectancy 40–60 years (developed world)[2]
Frequency	4.4 million (2015)[7]
Deaths	114,800 (2015)[8]

Contents

Signs and symptoms

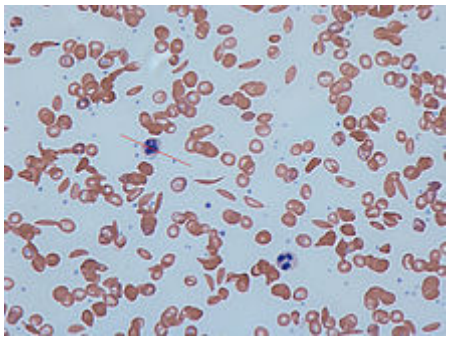
Signs of sickle cell disease usually begin in early childhood. The severity of symptoms can vary from person to person.[15] Sickle cell disease may lead to various acute and chronic complications, several of which have a high mortality rate.[16]



Sickle cell anaemia

Sickle cell crisis

The terms "sickle cell crisis" or "sickling crisis" may be used to describe several independent acute conditions occurring in patients with SCD, which results in anaemia and crises that could be of many types, including the vaso-occlusive crisis, aplastic crisis, sequestration crisis, haemolytic crisis, and others. Most episodes of sickle cell crises last between five and seven days.[17] "Although infection, dehydration, and acidosis (all of which favor sickling) can act as triggers, in most instances, no predisposing cause is identified."[18]



Sickle cells in human blood - both normal red blood cells and sickle-shaped cells are present.

Vaso-occlusive crisis

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid drug administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manages on nonsteroidal anti-inflammatory drugs such as diclofenac or naproxen. For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the penis[19] or lungs are considered an emergency and treated with red blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended.[20]

Splenic sequestration crisis

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected.[21] It is usually infarcted before the end of childhood in individuals suffering from sickle cell anaemia. This spleen damage increases the risk of infection from encapsulated organisms;[22][23] preventive antibiotics and vaccinations are recommended for those lacking proper spleen function.

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in haemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is supportive, sometimes with blood transfusion. These crises are transient; they continue for 3–4 hours and may last for one day.[24]

Normal blood cells next to a sickle blood cell, colored scanning electron microscope image

Acute chest syndrome

Acute chest syndrome is defined by at least two of these signs or symptoms: chest pain, fever, pulmonary infiltrate or focal abnormality, respiratory symptoms, or hypoxemia.[25] It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD. Most cases present with vaso-occlusive crises, and then develop acute chest syndrome.[26][27] Nevertheless, about 80% of people have vaso-occlusive crises during acute chest syndrome.

Aplastic crisis

Aplastic crises are acute worsenings of the patient's baseline anaemia, producing pale appearance, fast heart rate, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them.[28] Parvovirus infection almost completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of SCD patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease (causing reticulocytopenia), and the rapid turnover of red cells leads to the drop in haemoglobin. This crisis takes 4 to 7 days to disappear. Most patients can be managed supportively; some need blood transfusion.[29]

Haemolytic crisis

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in people with coexistent G6PD deficiency.[30] Management is supportive, sometimes with blood transfusions.[20]

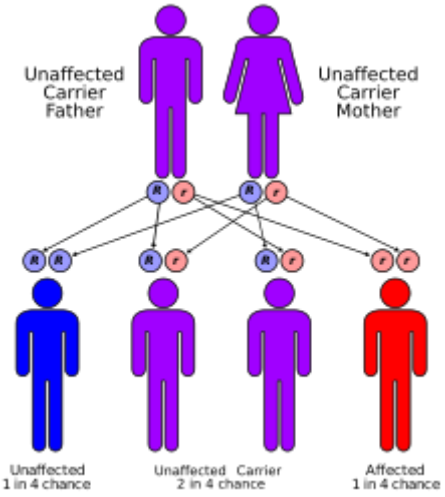
Other

One of the earliest clinical manifestations is dactylitis, presenting as early as six months of age, and may occur in children with sickle cell trait.[31] The crisis can last up to a month.[32] Given that pneumonia and sickling in the lung can both produce symptoms of acute chest syndrome, the patient is treated for both

conditions.[33] It can be triggered by painful crisis, respiratory infection, bone-marrow embolisation, or possibly by atelectasis, opiate administration, or surgery. Hematopoietic ulcers may also occur.[34]

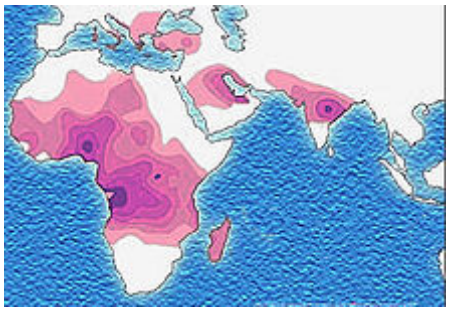
Genetics

Normally, humans have haemoglobin A, which consists of two alpha and two beta chains, haemoglobin A2, which consists of two alpha and two delta chains, and haemoglobin F, consisting of two alpha and two gamma chains in their bodies. Of these three types, haemoglobin F dominates until about 6 weeks of age. Afterwards, haemoglobin A dominates throughout life.[35] In people diagnosed with sickle cell disease, at least one of the β-globin subunits in haemoglobin A is replaced with what is known as haemoglobin S. In sickle cell anaemia, a common form of sickle cell disease, haemoglobin S replaces both β-globin subunits in the haemoglobin.[15]



Sickle cell disease is inherited in an autosomal recessive pattern.

Sickle cell conditions have an autosomal recessive pattern of inheritance from parents.[36] The types of haemoglobin a person makes in the red blood cells depend on what haemoglobin genes are inherited from her or his parents. If one parent has sickle cell anaemia and the other has sickle cell trait, then the child has a 50% chance of having sickle cell disease and a 50% chance of having sickle cell trait. When both parents have sickle cell trait, a child has a 25% chance of sickle cell disease; 25% do not carry any sickle cell alleles, and 50% have the heterozygous condition.[37]

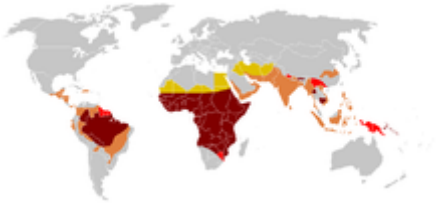

Distribution of the sickle cell trait, shown in pink and purple

Sickle cell gene mutation probably arose spontaneously in different geographic areas, as suggested by restriction endonuclease analysis. These variants are known as Cameroon, Senegal, Benin, Bantu, and Saudi-Asian. Their clinical importance is because some are associated with higher HbF levels, e.g., Senegal and Saudi-Asian variants, and tend to have milder disease.[38]


Historical distribution of malaria (no longer endemic in Europe), shown in green

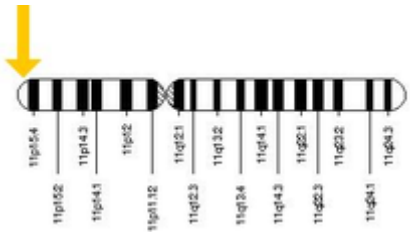
The gene defect is a single nucleotide mutation (see single-nucleotide polymorphism – SNP) (GAG codon changing to GTG) of the β-globin gene, which results in glutamic acid (E/Glu) being substituted by valine (V/Val) at position 6.[39][note 1] Haemoglobin S with this mutation is referred to as HbS, as opposed to the normal adult HbA. This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structures of haemoglobin in conditions of normal oxygen concentration. However, under low oxygen concentration, HbS polymerizes and forms fibrous precipitates because the deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices (Phe 85, Leu 88).[40]

In people heterozygous for HbS (carriers of sickling haemoglobin), the polymerisation problems are minor because the normal allele is able to produce half of the haemoglobin. In people homozygous for HbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth, doughnut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated.



Modern distribution of malaria

The allele responsible for sickle cell anaemia can be found on the short arm of chromosome 11, more specifically 11p15.5. A person who receives the defective gene from both father and mother develops the disease; a person who receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier or heterozygote. Heterozygotes are still able to contract malaria, but their symptoms are generally less severe.[41]



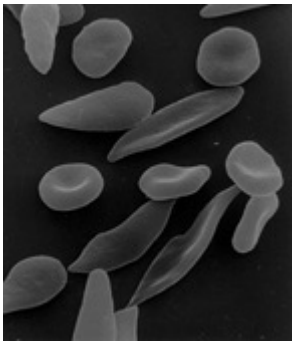
HBB gene (responsible for sickle cell anaemia) is located on the short (p) arm of chromosome 11 at position 15.5.

Due to the adaptive advantage of the heterozygote, the disease is still prevalent, especially among people with recent ancestry in malaria-stricken areas, such as Africa, the Mediterranean, India, and the Middle East.[42] Malaria was historically endemic to southern Europe, but it was declared eradicated in the mid-20th century, with the exception of rare sporadic cases.[43]

The malaria parasite has a complex lifecycle and spends part of it in red blood cells. In a carrier, the presence of the malaria parasite causes the red blood cells with defective haemoglobin to rupture prematurely, making the *Plasmodium* parasite unable to reproduce. Further, the polymerization of Hb affects the ability of the parasite to digest Hb in the first place. Therefore, in areas where malaria is a problem, people's chances of survival actually increase if they carry sickle cell trait (selection for the heterozygote).

In the United States, with no endemic malaria, the prevalence of sickle cell anaemia among people of African ancestry is lower (about 0.25%) than among people in West Africa (about 4.0%) and is falling. Without endemic malaria, the sickle cell mutation is purely disadvantageous and tends to decline in the affected population by natural selection, and now artificially through prenatal genetic screening. However, the African American community descends from a significant admixture of several African and non-African ethnic groups and also represents the descendants of survivors of slavery and the slave trade. Thus, a degree of genetic dilution via crossbreeding with non-African people and high health-selective pressure through slavery (especially the slave trade and the frequently deadly Middle Passage) may be the most plausible explanations for the lower prevalence of sickle cell anaemia (and, possibly, other genetic diseases) among African Americans compared to West Africans. Another factor that limits the spread of sickle cell genes in North America is the relative absence of polygamy. In polygamous societies, affected males may father many children with multiple partners.[44]

Pathophysiology



Scanning electron micrograph showing a mixture of red blood cells, some with round normal morphology, some with mild sickling showing elongation and bending

The loss of red blood cell elasticity is central to the pathophysiology of sickle cell disease. Normal red blood cells are quite elastic and have a biconcave disc shape, which allows the cells to deform to pass through capillaries.[45] In sickle cell disease, low oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia.

The actual anaemia of the illness is caused by haemolysis, the destruction of the red cells, because of their shape. Although the bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction.[46] Healthy red blood cells typically function for 90–120 days, but sickled cells only last 10–20 days.[47]

Diagnosis

In HbS, the complete blood count reveals haemoglobin levels in the range of 6–8 g/dl with a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). In other forms of sickle cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (HbS) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography. Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.[48]

An acute sickle cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be routinely performed.[49]

People who are known carriers of the disease often undergo genetic counseling before they have children. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used. Neonatal screening provides not only a method of early detection for individuals with sickle cell disease, but also allows for identification of the groups of people who carry the sickle cell trait.[50]

Management

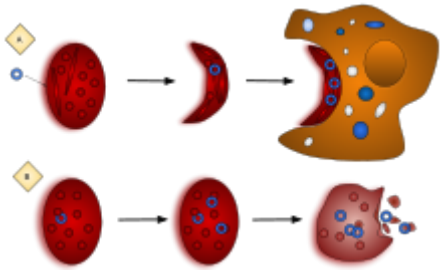
Treatment involves a number of measures. While it has been historically recommended that people with sickle cell disease avoid exercise, regular exercise may benefit people.[51] Dehydration should be avoided.[52] A diet high in calcium is recommended.[53] L-glutamine use was supported by the FDA starting at the age of five, as it decreases complications.[54]

Folic acid and penicillin

From birth to five years of age, penicillin daily, due to the immature immune system that makes them more prone to early childhood illnesses, is recommended.[55] Dietary supplementation of folic acid had been previously recommended by the WHO.[5] A 2016 Cochrane review of its use found "the effect of supplementation on anaemia and any symptoms of anaemia remains unclear" due to a lack of medical evidence.[56]

Malaria prevention

The protective effect of sickle cell trait does not apply to people with sickle cell disease; in fact, they are more vulnerable to malaria, since the most common cause of painful crises in malarial countries is infection with malaria. People with sickle cell disease living in malarial countries should receive lifelong medication for prevention.[57]



Possible advantage of being heterozygous for sickle cell anemia disease (A) vs. normal blood cell response (B) when infected with malaria

Vaso-occlusive crisis

Most people with sickle cell disease have intensely painful episodes called vaso-occlusive crises. However, the frequency, severity, and duration of these crises vary tremendously. Painful crises are treated symptomatically with pain medications; pain management requires opioid drug administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manages on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Diphenhydramine is also an effective agent that doctors frequently prescribe to help control itching associated with the use of opioids.

Acute chest syndrome

Management is similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since cell wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome),[58] oxygen supplementation for hypoxia, and close observation. In the absence of high quality evidence regarding the effectiveness of antibiotics for acute chest syndrome in people with sickle cell disease, there is no standard antibiotic treatment as of 2019.[59]

Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the person's red cell mass for normal red cells, which decreases the level of haemoglobin S in the patient's blood. The patient with suspected acute chest syndrome should be admitted to the hospital with worsening A-a gradient an indication for ICU admission.[25]

Hydroxyurea

Hydroxyurea probably reduces the frequency of painful episodes and the risk of life-threatening illness or death but there is currently insufficient evidence regarding the risk of adverse effects.[60] Hydroxyurea and phlebotomy combined may be more effective than transfusion and chelation combined in terms of

pain, life-threatening illness and risk of death.[60]

It was the first approved drug for the treatment of sickle cell anaemia, and was shown to decrease the number and severity of attacks in 1995[61] and shown to possibly increase survival time in a study in 2003.[62] This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and some concern exists that long-term use may be harmful, but this risk has been shown to be either absent or very small and the benefits likely outweigh the risks.[16][63]

Voxelotor was approved in the United States in 2019 to increase hemoglobin in people with SS disease.[64]

Blood transfusion

Blood transfusions are often used in the management of sickle cell disease in acute cases and to prevent complications by decreasing the number of red blood cells (RBCs) that can sickle by adding normal red blood cells.[65] In children, preventive RBC transfusion therapy has been shown to reduce the risk of first stroke or silent stroke when transcranial Doppler ultrasonography shows abnormal cerebral blood flow.[6] In those who have sustained a prior stroke event, it also reduces the risk of recurrent stroke and additional silent strokes.[66][67]

Bone marrow transplant

Bone marrow transplants have proven effective in children; they are the only known cure for SCD.[68] However, bone marrow transplants are difficult to obtain because of the specific HLA typing necessary. Ideally, a close relative (allogeneic) would donate the bone marrow necessary for transplantation.

Avascular necrosis

When treating avascular necrosis of the bone in people with sickle cell disease, the aim of treatment is to reduce or stop the pain and maintain joint mobility.[69] Current treatment options are to rest the joint, physical therapy, pain-relief medicine, joint-replacement surgery, or bone grafting.[69] High quality, randomized, controlled trials are needed to assess the most effective treatment option and determine if a combination of physical therapy and surgery is more effective than physical therapy alone.[69]

Psychological therapies

Psychological therapies such as patient education, cognitive therapy, behavioural therapy, and psychodynamic psychotherapy, that aim to complement current medical treatments, require further research to determine their effectiveness.[21]

Prognosis

About 90% of people survive to age 20, and close to 50% survive beyond age 50.[70] In 2001, according to one study performed in Jamaica, the estimated mean survival for people was 53 years for men and 58 years for women with homozygous SCD.[71] The specific life expectancy in much of the developing world is unknown.[72] In 1975 about 7.3% of people with SCD died before their 23rd birthday; while in 1989 2.6% of people with SCD died by the age of 20.[73]

Complications

Sickle cell anaemia can lead to various complications, including:

- Increased risk of severe bacterial infections is due to loss of functioning spleen tissue (and comparable to the risk of infections after having the spleen removed surgically). These infections are typically caused by encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for *S. pneumoniae*.[74]
- Stroke, which can result from a progressive narrowing of blood vessels, prevents oxygen from reaching the brain. Cerebral infarction occurs in children and cerebral haemorrhage in adults.
- Silent stroke causes no immediate symptoms, but is associated with damage to the brain. Silent stroke is probably five times as common as symptomatic stroke. About 10–15% of children with SCD suffer strokes, with silent strokes predominating in the younger patients.[75][76]
- Cholelithiasis (gallstones) and cholecystitis may result from excessive bilirubin production and precipitation due to prolonged haemolysis.
- Avascular necrosis (aseptic bone necrosis) of the hip and other major joints may occur as a result of ischaemia.[69]
- Decreased immune reactions due to hyposplenism (malfunctioning of the spleen)[77]
- Priapism and infarction of the penis[78]
- Osteomyelitis (bacterial bone infection), the most common cause of osteomyelitis in SCD is *Salmonella* (especially the atypical serotypes *Salmonella typhimurium, Salmonella enteritidis, Salmonella choleraesuis*, and *Salmonella paratyphi* B), followed by *Staphylococcus aureus* and Gram-negative enteric bacilli perhaps because intravascular sickling of the bowel leads to patchy ischaemic infarction.[79]
- Acute papillary necrosis in the kidneys
- Leg ulcers[80]
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages, and retinal detachments can result in blindness.[81] Regular annual eye checks are recommended.
- During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia
- Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have unreported chronic pain.[82]
- Pulmonary hypertension (increased pressure on the pulmonary artery) can lead to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance, and episodes of syncope. 21% of children and 30% of adults have evidence of pulmonary hypertension when tested; this is associated with reduced walking distance and increased mortality.[83]
- Chronic kidney failure due to sickle-cell nephropathy manifests itself with hypertension, protein loss in the urine, loss of red blood cells in urine and worsened anaemia. If it progresses to end-stage kidney failure, it carries a poor prognosis.[84]

Epidemiology

The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India, and the Middle East.[85] Migration of substantial populations from these high-prevalence areas to low-prevalence countries in Europe has dramatically increased in recent decades and

in some European countries, sickle cell disease has now overtaken more familiar genetic conditions such as haemophilia and cystic fibrosis.[86] In 2015, it resulted in about 114,800 deaths.[8]

Sickle cell disease occurs more commonly among people whose ancestors lived in tropical and subtropical sub-Saharan regions where malaria is or was common. Where malaria is common, carrying a single sickle cell allele (trait) confers a heterozygote advantage; humans with one of the two alleles of sickle cell disease show less severe symptoms when infected with malaria.[87]

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.[88]

Africa

Three-quarters of sickle cell cases occur in Africa. A recent WHO report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10 and 40% across equatorial Africa, decreasing to 1–2% on the North African coast and <1% in South Africa.[89] Studies in Africa show a significant decrease in infant mortality rate, ages 2–16 months, because of the sickle cell trait. This happened in areas of predominant malarial cases.[90]

United States

The number of people with the disease in the United States is about one in 5,000, mostly affecting Americans of sub-Saharan African descent.[91] In the United States, about one out of 365 African-American children and one in every 16,300 Hispanic-American children have sickle cell anaemia.[92] An estimated 100 thousand Americans have the disease.[92] The life expectancy for men with SCD is approximately 42 years of age while women live approximately six years longer.[93] An additional 2 million are carriers of the sickle cell trait.[94] Most infants with SCD born in the United States are identified by routine neonatal screening. As of 2016 all 50 states include screening for sickle cell disease as part of their newborn screen.[95] Sickle cell anemia is the most common genetic disorder among African Americans. Approximately 8% are carriers and 1 in 375 are born with the disease.[96]

Patient advocates for sickle cell disease have complained that it gets less government and private research funding than similar rare diseases such as cystic fibrosis, with researcher Elliott Vichinsky saying this shows racial discrimination or the role of wealth in health care advocacy.[97]

France

As a result of population growth in African-Caribbean regions of overseas France and immigration from North and sub-Saharan Africa to mainland France, sickle cell disease has become a major health problem in France.[98] SCD has become the most common genetic disease in the country, with an overall birth prevalence of one in 2,415 in metropolitan France, ahead of phenylketonuria (one in 10,862), congenital hypothyroidism (one in 3,132), congenital adrenal hyperplasia (one in 19,008) and cystic fibrosis (one in 5,014) for the same reference period.

Since 2000, neonatal screening of SCD has been performed at national level for all newborns defined as being "at risk" for SCD based on ethnic origin (defined as those born to parents originating from sub-Saharan Africa, North Africa, the Mediterranean area (South Italy, Greece, and Turkey), the Arabic peninsula, the French overseas islands, and the Indian subcontinent).[99]

United Kingdom

In the United Kingdom, between 12,000 and 15,000 people are thought to have sickle cell disease [100] with an estimated 250,000 carriers of the condition in England alone. As the number of carriers is only estimated, all newborn babies in the UK receive a routine blood test to screen for the condition.[101] Due to many adults in high-risk groups not knowing if they are carriers, pregnant women and both partners in a couple are offered screening so they can get counselling if they have the sickle cell trait.[102] In addition, blood donors from those in high-risk groups are also screened to confirm whether they are carriers and whether their blood filters properly.[103] Donors who are found to be carriers are then informed and their blood, while often used for those of the same ethnic group, is not used for those with sickle cell disease who require a blood transfusion.[104]

Middle East

In Saudi Arabia, about 4.2% of the population carry the sickle cell trait and 0.26% have sickle cell disease. The highest prevalence is in the Eastern province, where approximately 17% of the population carry the gene and 1.2% have sickle cell disease.[105] In 2005, Saudi Arabia introduced a mandatory premarital test including HB electrophoresis, which aimed to decrease the incidence of SCD and thalassemia.[106]

In Bahrain, a study published in 1998 that covered about 56,000 people in hospitals in Bahrain found that 2% of newborns have sickle cell disease, 18% of the surveyed people have the sickle cell trait, and 24% were carriers of the gene mutation causing the disease.[107] The country began screening of all pregnant women in 1992 and newborns started being tested if the mother was a carrier. In 2004, a law was passed requiring couples planning to get married to undergo free premarital counseling. These programs were accompanied by public education campaigns.[108]

India and Nepal

Sickle cell disease is common in some ethnic groups of central India,[109] where the prevalence has ranged from 9.4 to 22.2% in endemic areas of Madhya Pradesh, Rajasthan, and Chhattisgarh.[110] It is also endemic among Tharu people of Nepal and India; however, they have a sevenfold lower rate of malaria despite living in a malaria infested zone.[111]

Caribbean Islands

In Jamaica, 10% of the population carry the sickle cell gene, making it the most prevalent genetic disorder in the country.[112]

History

The first modern report of sickle cell disease may have been in 1846, where the autopsy of an executed runaway slave was discussed; the key finding was the absence of the spleen.[113][114] Reportedly, African slaves in the United States exhibited resistance to malaria, but were prone to leg ulcers.[114] The abnormal characteristics of the red blood cells, which later lent their name to the condition, was first described by Ernest E. Irons (1877–1959), intern to Chicago cardiologist and professor of medicine James B. Herrick (1861–1954), in 1910. Irons saw "peculiar elongated and sickle-shaped" cells in the blood of a man named Walter Clement Noel, a 20-year-old first-year dental student from Grenada. Noel had been admitted to the Chicago Presbyterian Hospital in December 1904 suffering from anaemia.[13][115] Noel was readmitted several times over the next three years for "muscular rheumatism" and "bilious attacks" but completed his studies and returned to the capital of Grenada (St. George's) to practice dentistry. He died of pneumonia in 1916 and is buried in the Catholic cemetery at Sauteurs in the north of Grenada.[13][14] Shortly after the report by Herrick, another case appeared in the *Virginia Medical Semi-Monthly* with the same title, "Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia."[116] This article is based on a patient admitted to the University of Virginia Hospital on November 15, 1910.[117] In the later description by Verne Mason in 1922, the name "sickle cell anemia" is first used.[14][118] Childhood problems related to sickle cells disease were not reported until the 1930s, despite the fact that this cannot have been uncommon in African-American populations.[114]

Memphis physician Lemuel Diggs, a prolific researcher into sickle cell disease, first introduced the distinction between sickle cell disease and trait in 1933, although until 1949, the genetic characteristics had not been elucidated by James V. Neel and E.A. Beet.[14] 1949 was the year when Linus Pauling described the unusual chemical behaviour of haemoglobin S, and attributed this to an abnormality in the molecule itself.[14][119] The actual molecular change in HbS was described in the late 1950s by Vernon Ingram.[14] The late 1940s and early 1950s saw further understanding in the link between malaria and sickle cell disease. In 1954, the introduction of haemoglobin electrophoresis allowed the discovery of particular subtypes, such as HbSC disease.[14]

Large-scale natural history studies and further intervention studies were introduced in the 1970s and 1980s, leading to widespread use of prophylaxis against pneumococcal infections amongst other interventions. Bill Cosby's Emmy-winning 1972 TV movie, *To All My Friends on Shore*, depicted the story of the parents of a child suffering from sickle cell disease.[120] The 1990s had the development of hydroxycarbamide, and reports of cure through bone marrow transplantation appeared in 2007.[14]

Some old texts refer to it as drepanocytosis.[121]

Society and culture

U.S. Social Security

Effective September 15, 2017, the U.S. Social Security Administration issued a Policy Interpretation Ruling providing background information on sickle cell disease and a description of how Social Security evaluates the disease during its adjudication process for disability claims.[122][123]

Research

Umbilical cord blood transplant

While umbilical cord blood transplant can potentially cure the condition, a suitable donor is available in only 10% of people.[124] About 7% of people also die as a result of the procedure and graft versus host disease may occur.[124]

Gene therapy

In 2001, sickle cell disease reportedly had been successfully treated in mice using gene therapy.[125][126] The researchers used a viral vector to make the mice—which have essentially the same defect that causes human sickle cell disease—express production of fetal haemoglobin (HbF), which an individual normally ceases to produce shortly after birth. In humans, using hydroxyurea to stimulate the production of HbF has been known to temporarily alleviate sickle cell disease symptoms. The researchers demonstrated that this gene therapy method is a more permanent way to increase therapeutic HbF production.[127]

Phase 1 clinical trials of gene therapy for sickle cell disease in humans were started in 2014. The clinical trials will assess the safety of lentiviral vector-modified bone marrow for adults with severe sickle cell disease.[128][129] As of 2018, however, no randomized controlled trials have been reported.[130] A case report for the first person treated was published in March 2017, with a few more people being treated since then.[131][132]

Gene editing platforms like CRISPR/Cas9 have been used to correct the disease-causing mutation in hematopoietic stem cells taken from a person with the condition.[133] In July 2019 the gene-editing tool CRISPR was used to edit bone marrow cells from a person with SCD to "turning on" the gene for fetal haemoglobin.[134]

Notes

1. Historic numbering put this glutamic acid residue at position 6 due to skipping the methionine (M/Met) start codon in protein amino acid position numbering. Current nomenclature calls for counting the methionine as the first amino acid, resulting in the glutamic acid residue falling at position 7. Many references still refer to position 6 and both should likely be referenced for clarity.

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External links

- Sickle cell (https://curlie.org/Health/Conditions_and_Diseases/Blood_Disorders/Sickle_Cell) at Curlie
- Sickle Cell Anaemia OER Project (http://www.sicklecellanaemia.org)

Classification	**ICD-10**: D57 (http://apps.who.int/classifications/icd10/browse/2016/en#/D57) · **ICD-9-CM**: 282.6 (http://www.icd9data.com/getICD9Code.ashx?icd9=282.6) · **OMIM**: 603903 (https://omim.org/entry/60390

	3) · **MeSH**: D000755 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D000755) · **DiseasesDB**: 12069 (http://www.diseasesdatabase.com/ddb12069.htm)
External resources	**MedlinePlus**: 000527 (https://www.nlm.nih.gov/medlineplus/ency/article/000527.htm) · **eMedicine**: med/2126 (https://emedicine.medscape.com/med/2126-overview) oph/490 (http://www.emedicine.com/oph/topic490.htm#) ped/2096 (http://www.emedicine.com/ped/topic2096.htm#) emerg/26 (http://www.emedicine.com/emerg/topic26.htm#) emerg/406 (http://www.emedicine.com/emerg/topic406.htm#) · **GeneReviews**: Sickle Cell Disease (https://www.ncbi.nlm.nih.gov/books/NBK1377/) · **Orphanet**: 232 (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=232)