Seminar

Sickle-cell disease

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Sickle-cell disease is an inherited blood condition common among, but not confined to, peoples of Equatorial African ancestry. The gene for sickle haemoglobin (HbS) results in the substitution of valine for the glutamic acid normally present at the sixth position from the amino terminus of the β chain of haemoglobin. This produces the different electrical charge used in detection of HbS by electrophoresis. It also changes the behaviour of haemoglobin molecules, which tend to polymerise on deoxygenation. As a consequence red blood cells become less pliable and some become deformed into the characteristic sickle shape. Inheritance of an HbS gene from one parent and normal β-globin gene from the other results in the harmless carrier state or sickle-cell trait.

Genetics

Sickle-cell disease is acquired by inheriting abnormal genes from both parents, the combination giving rise to different forms of sickle cell disease. Most common at birth is homozygous sickle-cell (SS) disease, also called sickle-cell anaemia, in which the HbS gene is inherited from both parents. Next in frequency among people of West African ancestry is sickle-cell/haemoglobin C (SC) disease, resulting from the inheritance of one HbS gene with one gene for HbC, which is the second most common abnormal haemoglobin gene in West Africa. Inheritance of the HbS gene with a gene for β-thalassaemia may cause either sickle-cell/β^+-thalassaemia with a mild clinical picture and 20–30% HbA or sickle-cell/β°-thalassaemia where there is no HbA and more severe disease. SS disease and sickle-cell/β°-thalassaemia tend to be severe and SC disease and sickle-cell/β^+-thalassaemia to be mild. The frequencies at birth are determined by the population frequency of the different genes and are illustrated for Jamaica in panel 1. Frequency at later ages is determined by survival, which tends to be better in the mild conditions.

The inheritance patterns are simple, If both parents carry one abnormal gene, there is a 1-in-4 chance that a child will have sickle-cell disease. The risk, of course, remains the same for each pregnancy regardless of the outcome of the previous one. If both parents have sickle-cell trait, there is a 75% chance of a healthy child at each pregnancy. If one parent has sickle-cell disease and their partner has the trait, then the risk of an affected child is doubled but if the partner is normal, the couple cannot have an affected child.

These simple genetic patterns indicate several options for preventing children being born with the disease.

Panel 1: **Frequency of major genotypes of sickle-cell disease at birth in Jamaica**

Genotype	Frequency
Homozygous sickle-cell disease	1 in 300
Sickle-cell/haemoglobin C disease	1 in 500
Sickle-cell/β^+thalassaemia	1 in 3000
Sickle-cell/β^0thalassaemia	1 in 7000

Populations informed and educated about the genetics of the disease and about their own genetic status may elect to avoid relationships between carriers. It may be feasible to incorporate this information into decisions in societies with arranged or first-cousin marriages where a choice of first-cousins is available. Even in established relationships between carriers, there is still a 75% chance of a healthy child at each pregnancy, and antenatal diagnosis may allow the parents to make an informed decision on completion of an affected pregnancy.

Epidemiology

Sickle-cell disease was first recognised in people of West African ancestry, giving rise to the common misconception that the illness was confined to this group. The sickle-cell trait occurs in 10–30% of peoples in Equatorial Africa but is infrequent in North and South Africa. The HbS gene is now known to be more widespread, occurring around the Mediterranean in Sicily and other parts of southern Italy, northern Greece, Turkey along the south-east coast, the north African coast, in Saudi Arabia especially the eastern province, and throughout central India. These are not insignificant foci. For example, the HbS gene is found at a frequency of 20–30% of people in some villages in northern Greece, 25% in the Qatif oasis of eastern Saudi Arabia, and in 20–30% of many communities in the Indian states of Orissa, Madhya Pradesh, and Maharastra. The main factor in this distribution is the occurrence of the HbS gene; a secondary factor is gene selection by falciparum malaria. People with the sickle-cell trait have a relative resistance to malaria so are more likely to survive, breed, and pass on their genes.

Studies of the structure of DNA surrounding the β-globin locus identifies several populations in whom the HbS mutation arose as a relatively recent event. These haplotypes[1] are known by the areas from which they were first described and the three major types in Africa are Senegal, Benin, and Bantu (or Central African Republic). The gene in Sicily, Greece, north Africa, and western Saudi Arabia is of the Benin haplotype and is believed to have reached these areas via the slave trade from west Africa. The gene in eastern Saudi Arabia and India has a different flanking structure. Known as the Asian haplotype,[2] it probably represents an independent occurrence of the HbS mutation.

Lancet 1997; **350:** 725–30

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Pathophysiology and clinical features

The polymerisation of deoxygenated HbS makes red blood cells less pliable and deforms some of them, and these stiff cells cannot easily negotiate capillary beds, resulting in premature destruction (haemolysis) and blockage of blood flow (vaso-occlusion). These two mechanisms result in a plethora of clinical manifestations (panel 2).

Haemolysis

The lifespan of a red blood cell is decreased from a normal 120 days to 10–12 days in most patients with SS disease. A new haematological equilibrium is formed with haemoglobin levels of 6–9 g/dL and reticulocyte counts of 5–15%. At steady-state haemoglobin levels, tissue oxygen deliver is near-normal because of the hyperdynamic circulation and the much lower oxygen affinity of HbS within the red cell.

Patients at steady-state Hb levels therefore do not complain of the symptoms typical of anaemia, and oxygen delivery may not be improved by transfusion. The rapid haemolytic rate demands significant increases in bone marrow activity, and some sites which normally shut down in infancy are still active in adults with severe forms of the disease. Requirements of folic acid are increased and shortage results in megaloblastic erythropoiesis[3] with low reticulocyte counts, increasing mean cell volume and falling haemoglobin. The metabolic demands of this expanded bone marrow for energy and protein may compete with the demands of the growth plates, impairing growth. Human parvovirus infection[4] destroys erythrocyte precursors causing the aplastic crisis with absent reticulocytes and a haemoglobin level which falls by about 1 g/dL per day. With prompt diagnosis and maintenance of oxygen delivery by transfusion, the outcome is predictable and benign since bone marrow activity always recommences after 7–10 days of aplasia.

Rapid haemolysis implies increased bilirubin excretion which is associated with clinical jaundice and increased formation of pigment gallstones. These gallstones are common, occurring in 40% of SS disease patients by the age of 20 years in the Jamaican cohort study. Specific symptoms, such as acute or chronic cholecystitis or obstruction of the common bileduct, are infrequent. In the cohort study, 77 patients are known to have had gallstones for periods of between 1 and 10 years, and cholecystectomy has been done in only 5 of them.

Panel 2: **Clinical consequences of haemolysis and vaso-occlusion in sickle-cell disease**

Haemolysis
Megaloblastic erythropoiesis
Aplastic crisis
Clinical jaundice and gallstones

Vasoocclusion
Splenic manifestations (pneumococcal septicaemia, splenic sequestration, hypersplenism)
Stroke
Sickle retinopathy
Impaired growth
Complications in pregnancy

Bone pain crises
Painful crisis
Dactylitis

Other
Acute chest syndrome
Genitourinary problems
Leg ulcers

Vaso-occlusion

Obstruction or impaired perfusion of blood vessels by stiff or sickled red cells may lead to ischaemia or necrosis of the tissue supplied, the symptoms being determined by the vessels affected. Central to much of the early pathology of sickle-cell disease is damage to the splenic vasculature by these poorly compliant cells. The spleen acts like a filter, removing damaged red cells and bacteria from the bloodstream. In sickle-cell disease the damaged red cells obstruct this filtration system, rendering children prone to overwhelming infections, especially pneumococcal septicaemia, acute enlargement (acute splenic sequestration), chronic enlargement (hypersplenism), and eventually a progressive splenic fibrosis and atrophy.

The risks of pneumococcal septicaemia may be reduced by prophylactic penicillin[6,7] and pneumococcal vaccine at later ages, although the increasing frequency of penicillin-resistant organisms and the development of a conjugated vaccine which may be effective in the first year of life may cause this prophylaxis to be modified.

Acute splenic sequestration may result in a sudden life-threatening fall in haemoglobin, requiring transfusion; the morbidity of recurrent events may be reduced by parental education,[8] and prophylactic splenectomy is usually recommended after two attacks. In chronic hypersplenism a more slowly developing sequestration results in a new haematological equilibrium with a mean red cell life of 2–4 days, very low haemoglobin levels (3–4 g/dL), raised reticulocytes (20–30%), and gross expansion of the bone marrow, the high energy demands of which complete with those of growth.[9] Some cases resolve spontaneously but others may need maintenance of haemoglobin levels by chronic transfusion or relief of hypersplenism by splenectomy. The risks of pneumococcal septicaemia and acute splenic sequestration are greater in the first 3 years of life and both become much less frequent after age 5 years. Chronic hypersplenism may occur as early as 1 year but is most common between 5 and 10 years and is unusual after 15 years.

Stroke is another devastating childhood problem occurring at a median age of 6 years, affects 8% by 14 years,[10] and is infrequent after this age. Hemiplegia is the commonest clinical pattern, and occlusion of major cerebral vessels has been reported in 80% of cases. There is a 50–70% chance of recurrence within 3 years of the first attack,[10,11] and treatment currently focuses on prevention of recurrence by chronic transfusion.[12] The many[1] problems with such programmes[13] make bone-marrow transplantation a viable option in suitable patients with compatible siblings. We need to know the risk factors for the first stroke and two initiatives are under study. These are the use of transcranial doppler[14] to detect cerebral stenoses that may precede strokes and studying the predictive role of upper airway obstruction, which has been reported as a potential risk factor.[15] Retinal ischaemia may precipitate proliferative sickle retinopathy which may cause vitreous haemorrhage with transient visual loss or retinal detachment with permanent blindness. The high prevalence of these complications in the mild genotypes SC disease and S/β^+-thalassaemia is puzzling. In controlled trials photocoagulating the

arterioles feeding these lesions have significantly reduced the frequency of vitreous haemorrhage but spontaneous autoinfarction is common and the role of treatment is not yet established.

Growth is affected, especially in SS disease, a subnormal weight developing in the first year and persisting throughout life. There is a lowered height velocity and attained height before puberty but puberty-associated growth persists for longer and the average final height may exceed that of controls. Sexual development is usually delayed, menarche by an average of 2·5 years in girls. Pregnancy carries increased risks of painful crises and acute chest syndrome especially in the last trimester and post-partum period, and this contributes to a maternal mortality rate of about 1%. There is an increased chance of fetal loss at each stage of pregnancy and a low birthweight, neither influenced by chronic transfusion during pregnancy. Patients requesting contraception should be given the most effective measures including oral, injectable depot preparations, intrauterine devices or, if a permanent method is desired, tubal ligation.

Bone pain crises

In adolescence and early adult life, the most severe problem is bone pain crisis resulting from avascular necrosis of active bone marrow. Although commonly referred to as the vaso-occlusive crisis, there is little evidence to support vaso-occlusion, and the frequent bilateral symmetrical pattern of bone pain, its precipitation by skin cooling which promotes vascular shunting rather than sickling, and its increased frequency in some conditions with decreased sickling are not consistent with this mechanism.[16] The hypothesis of a centrally mediated reflex shunting of blood flow away from the active bone marrow would have the same effect of inducing bone marrow necrosis and seems more consistent with the observations. Bone pain may be severe and affects most commonly the juxta-articular parts of the long bones, notably the knees, elbows, and shoulders, the ribs, spine and pelvis. Identifying precipitating factors may allow prevention of some painful crises; treatment of an established crisis involves rest, warmth, reassurance, rehydration, and pain relief. Jamaican experience suggest that most painful crises may be treated in a day-care centre, the patient returning home in the evening.

The paediatric counterpart of the painful crisis is hand-foot syndrome (dactylitis) which affects the small bones of the hands and feet in early childhood. This affects 50% of SS children by the age of 2 years, is commonly recurrent, and becomes rare after 5 years. It usually resolves completely although superimposed infection may cause premature epiphysial fusion and permanantly shortened, deformed small bones. Because of its early onset dactylitis commonly leads to the underlying diagnosis of sickle-cell disease if not already made at birth.

Other clinical manifestations

The acute chest syndrome is caused by a spectrum of pathology,[17,18] including elements of infection, infarction, pulmonary sequestration, and fat embolism,[19] and is a major cause of morbidity and mortality at all ages. Patients present with fever, cough, dyspnoea, and commonly pleuritic pain, with clinical evidence of consolidation and pulmonary infiltrates on radiology. The response to antibiotics may be slow. Some patients show rapid clinical and radiological deterioration with falling oxygen saturation levels and may respond dramatically to exchange transfusion. Avascular necrosis of the ribs with pleuritic pain and fever may cause voluntary splinting of the chest wall and secondary pulmonary collapse or consolidation,[21] the risk of which may be reduced by incentive spirometry.[22] Recurrent attacks of acute chest syndrome may result in pulmonary fibrosis and eventually chronic sickle lung disease.

Genitourinary problems include enuresis, chronic renal failure, and priapism. Damage to the vasa rectae system of the medulla impairs renal tubular function, limiting the concentration of urine, which contributes to nocturia and nocturnal enuresis. Progressive glomerular fibrosis and obsolescence, possibly related to glomerular hyperperfusion in childhood, causes chronic renal failure. Low erythropoietin levels lead to a falling haemoglobin which initially protects against painful crises but may lead to cardiac failure later on. Symptoms may be relieved by simple top-up transfusion, exogenous erythropoietin (although the dose is unclear), and renal transplantation. Sequestration within the corpora cavernosa results in priapism, stuttering nocturnal events affecting up to 40% of postpubertal Jamaican males. Major attacks lasting more than 24 hours may result in permanent damage to the vascular erectile system and impotence. Stuttering attacks are important as a prodrome to major events and may be prevented by oral stilboestrol.[23] Impotence may be treated by implantation of penile prostheses.

Chronic leg ulceration is a major cause of morbidity, affecting up to 75% of Jamaican adult SS patients. Developing most commonly in late adolescence and early adult life, ulceration has a serious impact on education and employment. Many ulcers stem from injury. Poor socioeconomic status contributes to the high prevalence in Jamaica, and this may explain the much lower frequency of leg ulcers in American and European patients.

Surgery and anaesthesia

Patients are more likely to require surgery and anaesthesia, and the ideal management remains controversial. In the USA and UK preoperative transfusion is common although its efficacy has not been shown in clinical trials. Postoperative morbidity in the Cooperative Trial in the USA[24] was not significantly less than in Jamaica, where routine preoperative transfusion is not employed.

Clinical severity

In general, SS disease and S/β^0-thalassaemia run severe courses and SC disease and S/β^+-thalassaemia are mild, but there may be striking variability within a single genotype. Some patients have multiple manifestations with a severe clinical course and death in childhood whereas others may reach the age of 70 with symptoms so mild that the diagnosis of sickle-cell disease is not suspected. Genetic factors modifying expression of SS disease include high levels of fetal haemoglobin (HbF) and α-thalassaemia. High levels of HbF protect against several clinical features[25] but the relation between HbF level and severity is not simple. Some patients with low HbF levels have mild courses while others in the Eastern Province of Saudi Arabia with high HbF level have frequent bone problems and painful crises. α-thalassaemia commonly coincides with sickle-cell disease, heterozygous

forms occurring in 35% of patients of African origin and in over 50% of patients in Saudi Arabia and India. This gene lowers the mean cell Hb concentration, inhibiting polymerisation of reduced HbS molecules and hence sickling and gives rise to a more mild clinical picture.[26] A high Hb level has also been recognised as a risk factor for painful crisis,[27,28] acute chest syndrome, hip necrosis and proliferative retinopathy.

Several mechanisms contribute to a high haemoglobin[29] which, if lowered by venesection, may prove a logical approach to prevention of the painful crisis. A randomised trial of venesection is underway in Jamaica. Only when (and if) this pilot trial demonstrates benefit will it be possible to address further questions such as the optimal Hb level to achieve.

Environmental factors also influence disease expression and higher socioeconomic status ameliorates disease. Psychosocial factors are likely to play a major role in disease severity and in coping mechanisms for recurrent pain, leg ulceration, and other features of a chronic disease. Firm data are required here because social and economic interventions have considerable potential in assisting patients to be more self-reliant and cope better with the disease.

In describing severity it is important to distinguish between recurrent morbidity which may not be life-threatening, such as chronic leg ulceration and frequent painful crises, and the cumulative end-organ damage of strokes, chronic pulmonary disease, and renal failure, which contribute to death. Despite advances in understanding of the disease, the inability to predict clinical severity remains a major deficiency in assisting the family's decision at the time of antenatal diagnosis and on defining the role of potentially dangerous therapies such as bone marrow transplantation.

Natural history and neonatal screening

The greatest mortality occurs in the first year of life which, considering the rarity of symptoms during the first 3–4 months because of the persistence of high levels of HbF, implies that the second 6 months is a very high risk period. Major causes of mortality at this age include pneumococcal septicaemia, acute splenic sequestration, aplastic crisis, and acute chest syndrome, some of which can be prevented or effectively treated if the underlying diagnosis is known. Neonatal screening and early diagnosis is essential to prepare preventive and management programmes. After the first year, the mortality falls but there is some evidence of a further peak in early adult life. In adolescence, leg ulceration and painful crises emerge as important causes of morbidity rather than mortality. Leg ulceration limits education and employment opportunities and typically runs a slowly healing/rapidly relapsing course often persisting for 5–10 years. Painful crises increase in frequency and severity between 15 and 25 years, in males, but after 30 years there is a progressive amelioration, and crises often cease after 40 years. Adolescence and young adult life is also the time of pregnancy-related problems, and although most women have relatively uneventful pregnancies, there is still a 1% mortality. After 40 years, many patients note improving quality of life although progressive pulmonary fibrosis and glomerular damage may limit survival.

Diagnostic and therapeutic advances

Antenatal diagnosis late in the first trimester may be performed by DNA analysis of fetal tissue obtained by chorionic villus sampling (CVS) or amniocentesis, CVS being feasible at an earlier stage of pregnancy (10–12 weeeks) but requiring specialist skills and carrying a greater risk of fetal loss. Either method can produce the fetal genotype within 48 hours but the inability to predict the likely clinical course of the child deprives the family of vital information in their decision on outcome of the pregnancy. As a result, 50–70% families elect to continue a pregnancy affected by SS disease, in contrast to the termination of almost all pregnancies affected by β-thalassaemia where a severe clinical course is predictable.

Inducing higher levels of HbF is a logical therapeutic objective, and the recently completed trial of hydroxyurea in the USA[30] showed significant reduction in painful crises and in transfusion requirements in selected severely affected SS adults. However, hydroxyurea has potential dangers in reducing white cell and platelet counts, must be carefully monitored and may have long-term effects. With these reservations it may play a role in some severe cases unamenable to other therapies such as avoiding precipitating factors, using diverting pastimes, developing self-reliance to cope more effectively with pain, and providing reassurance that the pain is not life-threatening. Some physicians may feel this is all too "soft", preferring to move swiftly on to an offer of something more dramatic such as bone-marrow transplantation. Nonetheless a lot can be achieved by these "low-tech" interventions.

Long-term transfusion programmes are hardly a new approach but with the easy availability of blood, matching facilities, and red cell exchange equipment, chronic transfusion is being increasingly utilised and for ever more arbitrary indications. Few physicians doubt the value of chronic transfusion in reducing recurrent strokes but extrapolation of its use to patients with abnormal MRI images of the brain or hip necrosis or to improve school attendance may exceed the risk-benefit ratio of this treatment. Even with plentiful supplies of blood and sensitive matching facilities, there are risks of red cell alloimmunisation, transfusion reactions, and transfusion-acquired infections, and these problems are compounded by iron overload and difficulties of venous access in chronic programmes.

Bone marrow transplantation (BMT) is another experimental approach to management of severe disease.[31] First used in a patient with SS disease who also had acute leukaemia,[32] BMT successfully treated both conditions and the patient is still alive and well 15 years later. Improvements in BMT now allow this to be considered for the treatment of SS disease alone and over 100 patients have been treated. The considerable cost, a short-term mortality of approximately 10%, the limited availability of HLA-compatible siblings, and the unknown long-term effects of the conditioning regimen on fertility and general health are likely to limit BMT to an experimental procedure.

The need for an animal model to study the problems of sickle-cell disease has resulted in the development of a variety of strains of transgenic mice.

General outlook

Calculations suggest that 250 000 children with SS disease are born each year worldwide, 100 000 in Nigeria alone. Faced with a problem of this magnitude, even the provision of simple medical care such as prophylactic penicillin or pneumococcal vaccine is daunting.

Prevention of the birth of SS children by widespread public education is the most logical approach although its impact has generally been limited and disappointing. Since the highest death rate occurs in the first year, early diagnosis is essential and is most easily performed at birth. Only then can the early life-saving interventions of prophylactic penicillin and parental education in the early detection of acute splenic sequestration be implemented. These two measures alone significantly improved survival in the Jamaican Cohort Study[33] and both are readily implemented in communities with limited resources where most of the disease occurs. Survival in SS disease is improving elsewhere and recent studies in the USA[34] predicted a mean survival of 42 years for males and 48 years for females. Learning to live with the disease, avoiding preventable complications, and having realistic expectations offer the best hope for survival and quality of life for the great majority of patients.

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