Sickle Cell Disease
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Introduction

The term sickle cell disease (SCD) includes a variety of pathological conditions resulting from the inheritance of the sickle hemoglobin (HbS) gene either homozygously or as a compound heterozygote with other interacting abnormal haemoglobin genes. The disease is clinically one of the most important haemoglobinopathies.

The most important protein of red blood cells (RBCs) is haemoglobin, which consists of four globin chains, each folded around a haem molecule. Haemoglobin delivers oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. The predominant haemoglobin in adulthood is HbA (±97%), which consists of two α- and two β- globin chains (α₂ β₂). Other haemoglobins are HbA₂ (2 to 3.5%; α₂ δ₂) and HbF (<2%; α₂ γ₂). During intrauterine development, several globin chains are synthesized (α, β, γ, δ, ε and ζ), with the predominant haemoglobin type during foetal life being HbF. In the first 12 weeks after birth, the HbF% quickly declines, leaving HbA and HbA₂ as the remaining haemoglobins (Schnog et al. 2004).

The β globin gene is found on chromosome 11. A single point mutation in the 6th codon leads to substitution of glutamic acid for valine, resulting in an abnormal globin: βs. This results in the formation of ‘sickle haemoglobin’, or HbS (α₂ βs₂). In haemoglobin C (HbC) the same nucleotide is changed where glutamic acid is substituted by lysine. In HbD Punjab, there is replacement of glutamine for glutamic acid at position β₁₂₁, and in HbO Arab the same codon is changed by the insertion of lysine (Serjeant GR and Serjeant BE 2001). These haemoglobins, when inherited with HbS, result in clinically significant SCD. SCD also results from the inheritance of HbS with genes for β-thalassaemias. The latter result from a wide variety of DNA mutations -that have in common, a reduced synthesis of globin chains. The more severe defects produce no normal β-chains and a generally severe syndrome called sickle cell-β0 thalassaemia with no HbA. Less severe β-thalassaemia mutations result in reduced but variable levels of β-chain synthesis and hence different levels of HbA.

The most common genotype is homozygous SS disease. S-Haemoglobin C (SC) disease, Sβ+ thalassaemia and Sβ0 thalassaemia are also relatively common. The sickle gene is found in African and non-African people in equatorial Africa, southern Italy, northern Greece, southern Turkey, the eastern province of Saudi Arabia and India. More recently it has also been seen in the Americas and Europe, as a result of migration of people originating from these former regions. People who carry just one βS mutation have the sickle cell trait (HbAS), and are generally asymptomatic. However there is emerging data which suggest that having sickle cell trait may be associated with increased risk for adverse health outcomes such as venous thrombosis and obstetric complications (Austin et al. 2007). The frequency of the sickle cell
trait (AS) has been estimated as high as 25% in Riyadh, Saudi Arabia; 31% in Parthenon, Greece; 38% in Southeast India and 40% in Central Africa (Serjeant GR and Serjeant BE 2001). WHO reports that each year about 300,000 infants are born with a haemoglobinopathy, 200,000 of whom are born in Africa (World Health Organization 2006). Whereas SCD occurs in 1 in 500 African-American births, in Jamaica it occurs in 1 in 150 births. Most countries do not have exact figures for SCD prevalence, but estimated suggest that there are 12,000 persons with SCD in United Kingdom (Streetly A et al. 1997) and about 72,000 in the United States (Bonds 2005).

**Clinical Features**

**General Features**

The primary cause of the clinical symptomatology of sickle cell disease is the intracellular polymerization of sickle hemoglobin (Hb S) that occurs when sickle erythrocytes are partially deoxygenated under the hypoxic conditions of the microcirculation (Poillon et al. 1998). This, in turn, makes sickle RBCs less deformable and ultimately results in the debilitating microvascular occlusions, haemolytic anaemia and chronic inflammation characteristic of the disease (Edwards et al. 2005).

The morbidity of SCD varies with genotype as well as within genotype. Patients with the homozygous SS disease and Sβ0-thalassaemia suffer greater morbidity and earlier mortality than patients with other genotypes (Manci et al. 2003; Platt et al. 1994). The life expectancy of patients with the homozygous SS disease is 42 years for males and 48 years for females in the US (Bonds 2005; Platt et al. 1994) and 53 and 58.5 years respectively in Jamaica (Wierenga et al. 2001); whereas for those with SC disease, it is 60 years in males and 68 years in females (Platt et al. 1994). Some of the established predictors of this phenotypic heterogeneity are the levels of HbF present, presence of α-thalassaemia, and the β-haplotype associated with the HbS gene (Steinberg 2005). However, there are likely other markers of disease severity that are yet to be identified fully.

The clinical manifestations of the disease are quite variable and include repeated painful vaso-occlusive, haemolytic, aplastic episodes, and sequestration crises. Complications affect various organs and systems mainly skeletal, genito-urinary, gastrointestinal, spleen, hepato-biliary, cardiopulmonary and central nervous system (Meshikhes and al-Faraj 1998). Neonatal screening and the introduction of prophylactic penicillin in early childhood has reduced mortality to less than 2% by 10 years of age (Bonds 2005). These changes in life expectancy have shifted the spectrum of clinical problems to an increased focus on chronic organ dysfunction in developed countries.

There is some age specific order to clinical manifestations where dactylitis, acute splenic sequestration and increased susceptibility to infection are common before age 5 years; painful crises, delayed growth and sexual maturation, and leg ulcerations and priapism become issues of concern starting in the adolescent period; and chronic end organ complications such as sickle nephropathy and chronic sickle lung disease with pulmonary hypertension become more manifest after age 30 years (Alexander et al. 2004).
**Painful Crises**

The hallmark clinical manifestation of SCD is the acute vaso-occlusive event, or painful episode. This unique type of pain can start as early as 6 months of age, recur unpredictably over a lifetime, and require treatment with opioids (Smith et al. 2005). In children, painful crises often present as dactylitis of the hands and feet (‘hand-foot syndrome’) and may result in premature closure of the affected epiphysis, leading to shortened deformed bones (Serjeant et al. 1994). Painful events are the top cause of emergency room visits and hospitalizations (Ballas 2005; Ballas and Lusardi 2005), and are also a measure of disease severity and predictor of early death in adults (Steinberg 2005). Sickle pain can be the prodrome of a serious and potential fatal complication of SCD in some patients (Ballas 2005).

**Infections**

There are several abnormalities of the immune system in persons with SCD. The early loss of splenic function, either as a result of splenic sequestration and subsequent splenectomy or as a result of ‘auto-splenectomy’, is a major component in conferring increased susceptibility to encapsulated organisms such as Strep Pneumoniae and Salmonella spp., and leading to e.g., pneumococcal sepsis especially in children under the age of 3 years. Before the advent of prophylactic penicillin administration, children with SCD were 30-600 times more prone to developing invasive pneumococcal disease, manifesting as septicemia or meningitis even (Halasa et al. 2007). There are also abnormalities of leucocyte function, complement, immunoglobulins and cell-mediated immunity (Serjeant GR and Serjeant BE 2001). White cell count is known to be a marker of severity in SCD and it is well known that part of the pathogenesis of vascular occlusion in SCD is due to increased leukocyte adherence to its endothelium (Okpala 2004).

**Effects on Major Organ Systems**

**The Respiratory System**

Pulmonary complications are one of the commonest set of complications in SCD. They are also a major cause of acute morbidity and mortality in SCD (Gray et al. 1991; Platt et al. 1994; A. N. Thomas et al. 1982). Acute chest syndrome (ACS) consists of a combination of signs and symptoms including dyspnoea, chest pain, fever, cough, multifocal pulmonary infiltrates on the chest radiograph, and a raised white cell count. It is a form of lung injury that can progress to adult respiratory distress syndrome (ARDS). It is estimated that half of all patients with sickle cell anaemia will develop ACS at least once in their lives, and ACS is the second most common cause of admission after painful vaso-occlusive crises (Mak and Davies 2003). Amongst the chronic cardiopulmonary complications of SCD, pulmonary hypertension has emerged as the major threat to the well-being and longevity of patients with SCD (Machado and Gladwin 2005).

**The Cardiovascular system**

Blood pressure is typically low in persons with SCD, and in fact what is a ‘normal’ blood pressure in non-SCD persons, may be clinically quite high for those with the disease (Grell et al. 1981; Homi et al. 1993; Johnson and Giorgio 1981; Pegelow et al. 1997). Various theories for this have been forwarded including defects in renal tubular sodium and water conservation, lowered peripheral vascular resistance, and stimulation of renal prostaglandin synthesis (Homi et
al. 1993). In addition, the expected age-related increases in blood pressure (Grell et al. 1981; Homi et al. 1993; Rodgers et al. 1993) is absent. Notwithstanding the concept of ‘relative hypertension’ in SCD has emerged where blood pressure levels considered otherwise normal in individuals without sickle cell disease have been reported to be associated with increased risk of stroke, as well as mortality. (Gordeuk et al. 2008; Pegelow et al. 1997; Rodgers et al. 1993). Additionally, increasing blood pressure is also an important predictor of chronic renal disease in SCD (Powars et al. 1991).

The chronic anaemia of SCD translated into higher cardiac output, cardiomegaly starting as early as age 5 years, and a systolic murmur which may be related to the increase in stroke volume (Covitz et al. 1995). Typically there is hypertrophy affecting both left and right ventricles (Serjeant GR and Serjeant BE 2001).

The liver and spleen
Acute splenic sequestration crisis is a life-threatening complication of homozygous SCD. It is rare in adults due to progressive splenic fibrosis as a result of repeated infarctions and occurs mainly in infants and young children aged less than 8 years (Solanki et al. 1986); 30% are under the age of 5 years (Emond et al. 1985). It may also occur in patients who have not developed splenic fibrosis and adult patients with sickle cell thalassaemia and sickle cell-haemoglobin C (Hb-SC) and also in patients with high levels of foetal haemoglobin, Hb-F (Serjeant 1970). These abnormalities in the splenic function also affect the immune status of patients with SCD, causing greater susceptibility to infections, especially with encapsulated organisms such as Strep Pneumoniae.

Multiple hepato-biliary complications occur in patients with SCD due to the increased risk of hepatic injury from sickling, cholelithiasis, choledocholithiasis and acute hepatic failure (Meshikhes and al-Faraj 1998). Patients with SCD are at high risk of developing pigmented gall stones due to chronic haemolysis. The incidence varies from one population to another and increases with age. The reported prevalence of gall stones in homozygous SCD (Hb-SS) varied from 34% to 70% (Cameron et al. 1971; Stephens and Scott 1980) in the United States, and was 29% in Jamaica and Africa (Billa et al. 1991; McCall et al. 1977).

The Musculoskeletal System
The painful crisis that has been described already can affect any part of the body, especially the extremities, back or chest. Its severity, location, and duration may vary within groups of patients and within each individual. Moreover, the frequency and severity of each pain crisis may change as a person grows from childhood to adulthood, with the break point being the late teens (Niscola et al. 2009). The frequency of the painful crises denotes the gravity of the sickling disorder; three or more crises annually indicate severe disease (Ballas 2005).

The increased susceptibility of sickle cell disease patients to infections, including osteomyelitis, has long been recognized with several mechanisms postulated including hyposplenism, impaired complement activity and the presence of infarcted or necrotic bone (Almeida and Roberts 2005). Osteomyelitis, particularly due to Salmonella, is also more common in SCD and may be seen at any age (Anand and Glatt 1994). Osteonecrosis or AVN occurs when vaso-occlusion results in the infarction of the articular surfaces and heads of the long bones. Avascular necrosis
of the femoral head leading to the destruction of the hip joint may be seen as early as the first
decade of life and in some cases requires joint replacement.

Leg ulcers are common in SCD (Cumming et al. 2008; Koshy et al. 1989; Serjeant 1974;
Serjeant et al. 2005), although rare before the age of 5 years. It is estimated that 8-10% of
homozygous SS patients will develop leg ulceration between 10 and 50 years of age, but higher
rates of more than 50% have been reported (Koshy et al. 1989; Serjeant 1974). The incidence
of leg ulceration in tropical countries is further complicated by the high frequency of tropical and
chronic non-specific ulcers (Akinayanju and Akinsete 1979). In Jamaica, venous incompetence,
low socioeconomic status, and high serum LDH have been shown to be the strongest predictors
of chronic ulceration (Cumming et al. 2008). The ulcers occur spontaneously or as a result of
local trauma with subsequent infection and skin necrosis but no specific organisms have been
incriminated. Leg ulcers can prevent patients from undertaking many forms of manual work and
significantly decrease their independence (Mohan et al. 2000).

The Nervous System
Cerebrovascular accidents occur in 8 to 17% of patients with SS disease, cerebral infarction
being more common in children and intracranial haemorrhage commoner in adults. The overall
incidence of first overt infarction in HbSS patients by age 20 years is 11% and by age 45 years is
24% (Wong and Powars 2005). The risk for cerebrovascular accidents can be predicted by
trans-cranial Doppler ultrasonography, a non-invasive, out-patient procedure to measure time-
average mean velocity (TAMV) of blood in cerebral vessels (Adams 2005). Patients with an
abnormal TAMV, defined as \( \geq 200 \text{ cm/s} \), have a 43-fold increased stroke risk when compared to
those with TAMV < 200 cm/s.

Neurocognitive dysfunction has been shown to exist in children with SCD, with behavioural
problems, low self-esteem and disturbances in body image perception being more evident in
them (Brown et al. 1993a). Developmental processes may be a little slower in children with
SCD as well, and the presence of clinically silent brain damage has been documented (Serjeant
GR and Serjeant BE 2001). Silent infarcts have been reported to signal future cerebrovascular
events.

The Genito-Urinary System
Priapism is a painful failure of detumescence which could be due to excess release of contractile
neurotransmitters, obstruction of draining venules, malfunction of the intrinsic detumescence
mechanism, or long-lasting relaxation of intracavernosal smooth muscle (Serjeant GR and
Serjeant BE 2001). Low-flow priapism is more common, and is associated with a reduction in
venous outflow, hypoxia, acidosis, stasis, and tissue ischaemia. Clinical presentation of priapism
involves either scattered episodes, or a stuttering pattern, usually nocturnal, in which
progressively more intense episodes cluster over a short time. A sustained attack of priapism can
lead to impotence (Stuart and Nagel 2004).

Renal involvement, known as sickle nephropathy, similar to that seen in diabetic nephropathy is
common in sickle cell disease (Ataga and Orringer 2000), and at older ages is a major cause of
illness and death (A. N. Thomas et al. 1982). Microalbuminuria has been reported in 6.2% of
pediatric patients with HbSS genotype; but 10% in teenagers with HbSS (Wigfall et al. 2000).
In adults, the prevalence rises to 17-49% of those with HbSS genotype (Falk et al. 1992; Sesso et al. 1998). The clinical relevance and the pathogenic mechanism(s) underlying MA in sickle cell anaemia are unclear but increased glomerular filtration rate (GFR) and renal plasma flow (RPF) are noted in early years in individuals with SCD (Allon 1990; Schmitt et al. 1998). It has been proposed that this hyper-filtration leads to gradual sclerosis of the glomerular capillaries and predisposes to renal insufficiency in these patients (Ataga and Orringer 2000; Schmitt et al. 1998).

As health status in SCD improves, pregnancy is increasingly being seen and managed in the patient with SCD. However, there are still trends for increased maternal mortality, intrauterine growth retardation, low fetal birth weights, prematurity, etc. in these pregnancies (Powars et al. 1986; Serjeant et al. 2004).

It is evident that the disease can have protean manifestations, and hence generalists, haematologists, internists and paediatricians all need to be knowledgeable about its clinical presentations and the management of these presentations.

**Psychosocial effects**

In assessing the seriousness of this disease, no one should underestimate its emotional and social impact. The patient endures not only the pain itself but also the emotional strain from unpredictable bouts of pain, fear of death, and lost time and social isolation at school and work (Barbarin et al. 1994; Barrett et al. 1988). It is also known that psychological and social factors contribute substantially to complaints of pain. Sociodemographic factors such as race, gender, age, education, and socioeconomic status as an index of attained wealth, as well as general psychological factors such as coping style, coping capacity, and social support, have been used to explain differences in disability associated with pain intensity, pain threshold, and pain tolerance, both clinically and in research settings.

These problems continue over the years, and both children and adults with sickle cell disease often suffer from depression (M. Asnani 2004; Wilson Schaeffer et al. 1999). The financial costs of medical treatments combined with lost work can be very burdensome. Any chronic illness places stress on the patient and family, but sickle cell patients and caregivers often face great obstacles in finding psychological support for the disease (Dorsey et al. 2001; Maxwell et al. 1999).

Sickle cell disease carries a huge psychosocial burden impacting on physical, psychological, social and occupational well-being as well as levels of independence (Anie and Steptoe 2003; Anie et al. 2002b; Bodhise et al. 2004; Jacob 2001; Kater et al. 1999; Ohaeri et al. 1995; Strickland et al. 2001; V. J. Thomas and Taylor 2002; Wison Schaeffer et al. 1999). Psychological complications in patients with SCD mainly result from the impact of pain and symptoms on their daily lives and society’s attitudes towards them (Anie 2005; Maxwell et al. 1999; Midence et al. 1993). Anie et al (Anie et al.) have shown that society’s attitudes and perception not only have a psychological impact on patients with SCD, but that health beliefs can be influenced by their culture, family support and work responsibility. Studies have shown increased anxiety, depression, social withdrawal, aggression, poor relationships and poor school performance (Brown et al. 1993a; Brown et al. 1993b; Burlew et al. 2000; Fuggle et al. 2002).
A few case reports also indicated high levels of parental anxiety, overprotection, excessive feelings of responsibility and guilt (Graham et al. 1982; Strickland et al. 2001; Whitten and Fischhoff 1974).

### Coping and Adjustment

SCD is a huge stressor to which both the one afflicted with it as well as his/her family and friends will potentially have difficulties adjusting and coping with. As pain is a longstanding complication in SCD, coping with pains and employment of different strategies to cope have been shown to predict adjustment and severity of pain (Gil et al. 1989). Thompson et al (Thompson et al. 1992) have demonstrated a high level (56%) of poor adjustment in their study sample. they did show however that those with good adjustment had better family support, lower levels of perceived stress, lower negative thinking/passive adherence pain-coping strategies and higher efficacy. Their counterparts in the United Kingdom (Anie et al. 2002b) have also demonstrated psychological coping patterns to be related both to pain experiences as well as to broader adjustment issues. Children with SCD exhibit lower adjustment and behavioural problems than adolescents (Hurtig and White 1986) and boys have greater problems than girls.

### Quality of Life

Studies have been conducted looking at painful crises, coping, work and social activities, and quality of life (QOL) in adult patients with SCD in UK and USA (Anie et al. 2002b; Gil et al. 1992; Ohaeri et al. 1995; Strickland et al. 2001). Some common complaints identified have been the limitations illness placed on social life; depressive feelings; abnormal habitus; suicidal ideation during crises; and the burden of illness on the family (Ohaeri et al. 1995; Strickland et al. 2001). Adults with sickle cell disease have reported poorer quality of life in comparison with the general population. The role limitations due to physical and emotional problems, lack of vitality and poor general health perceptions have been particularly marked. Some of these impairments are similar to those found in other chronic painful conditions, as the comparisons with haemochromatosis indicated (Anie et al. 2002b). The recently reported study on QOL in the PiSCES (Pain in Sickle Cell Epidemiology Study) group (McClish et al. 2005) has also found that SCD patients experience health related quality of life worse than the general population. In Jamaica, persons living in rural areas have reported better QOL than those in urban areas (M. R. Asnani et al. 2008), and this probably results from stronger social support mechanisms available to the former.

### Management

Management of SCD requires a comprehensive, multidisciplinary approach, and involves managing not only the patient, but also the family as well as others who may be affected by the patient’s illness. The components of comprehensive care include patient/parent information, genetic counselling, social services, prevention of infections, dietary advice and supplementation, psychotherapy, renal and other specialist medical care, maternal and child health, orthopaedic and general surgery, pain control, physiotherapy, dental and eye care, etc. (Okpala et al. 2002).
Health Maintenance

Education
For decades, complications of SCD produced the highest mortality rate in the first 3 years of life (Leikin et al. 1989). Early diagnosis of SCD, with prenatal diagnosis and neonatal screening, is crucial to implementing life saving measures early in the life of the affected infant. Widespread neonatal screening programmes, when linked to timely diagnostic testing, parental education especially with respect to recognizing early symptoms and signs of illness, and comprehensive care, have been shown to be effective in markedly improving survival in SCD (King et al. 2007; Schnog et al. 2004). Once the diagnosis of SCD is confirmed, a counselling and educational session should be held with the parents. All information cannot be delivered at the first session but it will set the tone for future consultations. Genotype specific information is provided at this session. Nutritional counselling, management of fever and painful episodes, academic and vocational counselling, pregnancy and other reproductive issues all need to be addressed. Children should be given more frequent routine appointments than adults who should be seen at least twice yearly.

Prevention of Infections
The most important intervention, to be started at age 4 months, is the implementation of penicillin prophylaxis, whether with twice daily oral penicillin or 4-weekly intramuscular benzathine penicillin, to prevent pneumococcal infections. This is given to age 4 years at which time the pneumococcal vaccine is given, and this regime has been shown to improve outcomes (Knight-Madden and Serjeant 2001). By providing instructions to patients and caregivers about splenic palpation and assessment of worsening pallor there have been marked improvements in mortality rates from splenic sequestration crises and aplastic crises respectively (Steinberg 1999).

Other steps to ensure prevention of infection include strict attention to hygiene, regular hand-washing, and avoidance of ingesting poorly cooked or contaminated foods, especially chicken and egg which may be implicated in Salmonella infections. Of course, proper complete immunizations need to be administered throughout the lifetime of persons with SCD. Other than the pneumococcal vaccine, other vaccines that are important are Haemophilus Influenzae, Neisseria meningitides, Hepatitis B and Influenza (Booth et al.).

Contraceptive & reproductive health counselling
Women with SCD should be advised and encouraged to use the most dependable forms of contraception available to them. Pregnancy in SCD needs to be managed in high-risk antenatal clinics and routine supplementation with folic acid and prenatal vitamins is recommended. Management of acute painful or acute chest crises is similar to that in the non-pregnant state. The last trimester and early postpartum periods are especially prone to complications with acute chest syndrome and sepsis. The benefits of prophylactic transfusions to prevent crises and other complications during pregnancy have not been proven, and current evidence suggests that improved pregnancy outcomes that are being achieved are due more to general improvements in pregnancy management than to transfusion therapy (Serjeant GR and Serjeant BE 2001).
Treatment modalities

Hydroxyurea
Hydroxyurea, a ribonucleotide reductase inhibitor, has been used to reduce the incidence of painful crises and acute chest syndrome, as well as the need for transfusion in those with more severe disease. Even though it has been shown to be effective in both paediatric and adult patients, it is not without multiple side-effects and requires close monitoring of the patient. Its precise role and effects in certain populations such as stroke prevention and organ preservation is still being established (Wiles and Howard 2009).

Transfusion therapy
Blood transfusions are used to raise the oxygen carrying capacity of blood and decrease the proportion of sickle red cells. Clinically, they will improve microvascular perfusion of tissues. Transfusions usually fall into two categories: episodic, acute transfusions to stabilize or reverse complications, and long-term, prophylactic transfusions to prevent future complications (Ohene-Frempong 2001). Chronic transfusion therapy is indicated when avoidance of potentially serious medical complications justifies the risks of alloimmunization, infection, and iron overload.

Stem cell transplantation
Haemopoietic cell transplantation is the only available potentially curative therapy for sickle-cell disease.

Estimated risk of death from HLA-identical-stem-cell transplantation in the disease is 5%. The goal is to successfully replace the host’s marrow with normal genotype cells before development of organ dysfunction (Stuart and Nagel 2004). Gene therapy has been explored in animal models and has shown some success, but is not likely to benefit patients in the near future.

Management of acute clinical syndromes

Painful Crises
As stated earlier, the painful crisis is a key manifestation of the disease and may affect individuals from as early as infancy. Patients should be advised to learn their trigger factors, the common ones being dehydration, infections, stress, and exposure to excessive cold. Most pain crises are managed at home (Stuart and Nagel 2004) and pain relieving measures are taught to the patient, including starting analgesics quickly, keeping warm, employing relaxation techniques and drinking fluids. Clinical management includes rapid administration of analgesics (with optimal dosing and frequent repeat dosing as dictated by response, and tailored to what has worked for the patient in the past), mainly opioids, treatment of underlying infections if needed, oxygen supplementation and rest. Use of incentive spirometry and advice about deep breathing exercises is crucial, especially with presence of chest pains, to prevent complications with acute chest syndrome or pneumonia. Hydroxyurea therapy has proven to be beneficial in reducing frequency of painful crises in homozygous SCD.
Acute chest syndrome
Acute chest syndrome is also a frequent cause of morbidity and mortality in SCD, and multiple episodes may lead to chronic lung disease and pulmonary hypertension. Antibiotics including macrolides, liberal use of analgesics and incentive spirometry are mainstay of treatment. Supplemental oxygen therapy and simple or exchange transfusions will need to be employed for more severe cases (Stuart and Nagel 2004). Those who continue to deteriorate despite an exchange transfusion may require intubation and positive-pressure ventilation. Fat embolism, especially to the central nervous system and to other multiple sites in the body can prove to be fatal.

Stroke
After acute chest syndrome, stroke is the most common killer of patients with SCD who are over three years of age. Between 8% and 10% of patients suffer strokes, typically at about age seven (Serjeant GR and Serjeant BE 2001). Stroke prevention has benefited from non-invasive testing to assess cerebral blood flow by transcranial Doppler velocity measurements that detect areas of vascular narrowing (Stuart and Nagel 2004). Immediate exchange transfusion at onset of stroke followed by a chronic transfusion programme has shown benefit in reducing recurrence of stroke.

Acute splenic sequestration
The most common complication leading to acute exacerbation of anemia is splenic sequestration. Caregivers should be taught splenic palpation at each visit to the physician. The immediate treatment of acute splenic sequestration (ASS) is directed toward correction of hypovolemia with red blood cell transfusion. Because severe ASS can be fatal within a few hours, emergency transfusion is required. Once a recurrence of the sequestration occurs, splenectomy is usually advised.

Priapism
Priapism must be treated to prevent partial or complete impotence, which can result from erections that last several hours to days. Drugs used to prevent priapism include terbutaline and phenylephrine, which help restrict blood flow to the penis and hormonal treatments, such leuprolide and diethylstilbestrol, which may prevent repetitive and prolonged episodes. Surgical procedures including direct aspiration of the corpora and shunting procedures may need to be employed to alleviate a major attack of priapism (Serjeant GR and Serjeant BE 2001).

Other acute anemic episodes
Hemolysis associated with SCD can have diverse manifestations. Chronic hemolysis leads to increased frequency of jaundice and pigmented gallstones in this population. Surgery is not recommended unless there are complications of cholelithiasis. Aplastic anemia can result especially after a bout of Human Parvovirus B19 infection, where erythropoiesis ceases temporarily and may be life-threatening if not managed urgently. Although most patients will resolve spontaneously, they need to be monitored closely as some will require blood transfusion.
Management of chronic complications

**Leg ulcers**

Leg ulcerations, even though not life-threatening can cause severe disability and psychosocial effects on those afflicted due to their chronicity (Serjeant 1974). Simple treatment with moist dressings, rest with elevation of the affected leg and elastic compression bandaging are usually effective. Some of the more severe cases will require skin grafting.

**Sickle nephropathy**

As life expectancy increases, chronic organ dysfunction becomes a greater problem in SCD. Renal insufficiency has emerged as one of the most prevalent forms of end organ failure occurring in these patients. Early renal impairment is usually clinically silent but microalbuminuria and changes in glomerular filtration rate are early functional markers. The use of angiotensin converting enzyme (ACE) inhibitors which reduces glomerular hyperfiltration have been found to be effective in reducing proteinuria in SCD, at least in short-term studies (Falk et al. 1992). Non-steroidal anti-inflammatory use has to be limited once renal dysfunction is detected.

**Sickle Retinopathy**

Patients with SCD are also more prone to retinopathy and need annual eye examinations. Once proliferative retinopathy develops, treatment is needed as they are then at risk of bleeding and retinal detachment. Techniques such as diathermy, cryotherapy and laser photocoagulation have been used to cause involution of neovascular lesions.

**Cardiopulmonary dysfunction**

No standard treatment exists for pulmonary hypertension in SCD. Those who are symptomatic may be treated in the same way as those without SCD, with intravenous prostacyclins, sildenafil and bosentan (Benza 2008). However, no clinical studies have validated these treatment modalities to date. Maximization of the primary pathology, i.e. SCD, is of course mandatory and use of Hydroxyurea may be beneficial in pulmonary hypertension as well (Machado and Gladwin 2005).

Congestive heart failure as a result of worsening anemia tends to respond well to diuretics and intermittent red cell transfusions. Digoxin and diuretics are employed to manage it if there is no fall in haemoglobin.

**AVN**

Avascular necrosis especially of the hip is a chronic debilitating condition which requires, in the early stages, analgesics and reduced weight bearing. However, hip arthroplasty is required for those with advanced disease who are severely symptomatic.

**Management of psychosocial issues**

It is important for health care professionals to understand the various psychosocial issues, such as coping, stress, depression, and reduced quality of life, which are important considerations for anyone living with a chronic illness. As no cure is possible for SCD, it is recommended that
psychological interventions should be incorporated into protocols for the management of patients and offered as standard care (Anie 2005). Offering education to improve knowledge and understanding can help patients to cope better with the various manifestations of their illness. Cognitive and behavioural therapy, whose aim is to enable people suffering from chronic illness to develop core skills and techniques necessary to take good care of themselves, has been shown to reduce health service utilization in both children and adolescents with SCD (Anie et al. 2002a), and in adults reduces pain (V. Thomas 2000), improves mood and psychological coping ability.

**Future Directions**

As the role of inflammation and endothelial dysfunction in the pathophysiology of SCD becomes clearer, advances in further treatment modalities can be anticipated. Therefore, antiadhesion and anti-inflammatory therapies may have a role in management of this disease. Other treatment modalities such as role of nitric oxide, stem cell transplantation and gene therapy are all in experimental stages.

Clinically, the challenge of management of this disorder now needs to move more to early assessment and treatment of vital end-organ complications as the population of people with SCD ages. The study of the inherent variations of the phenotypic expressions of this disease in various geographically distinct populations of the world could also assist in elucidating mechanisms of the disease processes within SCD.

**References**


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