Sickle cell disease

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Introduction

Sickle cell disease is an inherited condition that is common among, but not confined to, peoples of African ancestry. It results from an abnormality in the β-chain of adult haemoglobin (HbA). The amino acid valine replaces the glutamic acid normally present at the sixth position from the amino terminus. This substitution changes the electrical charge of sickle haemoglobin (HbS) and causes the electrophoretic difference that is used to detect it. This change also leads to the molecule’s polymerization on deoxygenation, deforming the red cell into the sickled shape. Since β-chain synthesis is detectable early in fetal life, the condition may be diagnosed at 10-12 weeks of pregnancy. High levels of β-chain and hence HbS are not produced until 3-6 months of postnatal life so symptoms of the disease are unusual before 3 months.

Worldwide distribution of the HbS gene

The gene has become common because people who inherit one abnormal gene (the sickle cell trait) are relatively resistant to malaria at a critical stage in early childhood. This confers a survival advantage on the sickle cell trait that results in its increased frequency in malarious areas. The most malarious area of the world is Equatorial Africa where the sickle cell trait occurs in 10-25% of many of the areas’ populations. From West Africa the gene spread around the Mediterranean to Sicily and Southern Italy, Northern Greece, South East Turkey, and Western Saudi Arabia, across the Atlantic to North and South America and the Caribbean, and most recently to Northern Europe [1]. Studies of the DNA surrounding the β-globin locus suggest three independent occurrences of the sickle cell gene in Africa [2]. These are named after the areas where they were first described, Benin, Senegal, and Central African Republic or Bantu. Each therefore is a distinct haplotype. A separate independent occurrence of the sickle cell gene (the Asian haplotype) causing a disease with some differences from the African types occurs in the eastern Province of Saudi Arabia and throughout central India [3].

Nomenclature

Inheritance of the gene for HbS from one parent and a normal gene for HbA from the other results in the sickle cell trait (AS genotype). This does not result in sickle cell disease. The term sickle cell disease embraces several genotypes of which the most common and generally most severe is homozygous sickle cell disease (SS). Inheritance of the sickle cell gene with that for HbC (the second commonest abnormal haemoglobin among people of West African ancestry) results in sickle cell-HbC disease (SC). The inheritance of the sickle cell gene with that for β°-thalassaemia results in sickle cell-β° thalassaemia, a severe condition similar to SS disease, whereas inheritance of the β+-thalassaemia gene results in sickle cell-β+ thalassaemia, a mild condition similar to SC disease. The relative frequency of these conditions at birth is determined by the gene frequencies in the population. In Jamaica, SS disease occurs once in every 300 births, SC disease once in every 500 births, sickle cell-β+ thalassaemia once in every 3000 births and sickle cell-β°-thalassaemia once in...
every 7000 births. The differential diagnosis of the genotypes is summarised in Table I.

The haematological findings that are characteristic of the clinically well “steady state” vary markedly among individuals and genotypes. In SS disease, HbS within the red cell has a low affinity for oxygen [4]. Thus it releases more oxygen in the periphery than does HbA. For this reason patients rarely complain of classic anaemic symptoms at their steady state haemoglobin level. This observation implies that transfusing patients at their steady state haemoglobin level may achieve little or nothing in terms of oxygen delivery [5]. In any case, knowledge of the steady state haemoglobin level is important information for patient management.

Pathophysiology

Deformed or sickled red cells have difficulty negotiating the capillary beds. They are destroyed prematurely (haemolysis) and block flow in blood vessels (vaso-occlusion). In SS disease, rapid red cell destruction causes a mean red cell survival of 10-12 days [4] compared to 120 days in a normal individual, and usually results in anaemia (Hb 6-9 g/dl). Increased bilirubin production causes jaundice and pigment gallstone formation. The bone marrow is markedly expanded and has increased metabolic demands. The rapidly dividing red cell precursors are vulnerable to destruction by human parvovirus causing the aplastic crisis.

The filtering function of the spleen is compromised rendering patients prone to infections by encapsulated organisms especially pneumococci. Sequestration of red cells may occur within the spleen acutely (acute splenic sequestration), or chronically (hypersplenism). The vascular damage to the spleen finally results in a progressive splenic fibrosis. Avascular necrosis of the active bone marrow in the small bones of the hands and feet occurs in early childhood (dactylitis or hand-foot syndrome), juxta-articular areas of the long bones, spine, and pelvis (the painful crisis) and in the femoral head (femoral head necrosis) in later childhood and early adult life. Secondary infection of necrotic bone marrow especially by salmonella organisms is a common cause of osteomyelitis. Pulmonary involvement is common and referred to as the acute chest syndrome. Vascular damage to the skin around the ankles causes chronic leg ulcers in adolescents and sequestration in the corpora cavernosa causes priapism. In the retina this condition leads to proliferative retinopathy, and in the brain it results in strokes. Growth and development usually are retarded.

Clinical features

Acute anaemia

An acute life-threatening anaemia may occur with acute splenic sequestration and aplastic crisis. Acute splenic sequestration usually occurs between 4 months and 5 years of age. In the Jamaican Cohort Study [6], it affected 30% of SS children by 5 years, and is a common cause of death. Its aetiology is unknown, but splenic enlargement traps circulating red cells causing the haemoglobin to fall by 2-6 g/dl within periods as short as 3 hours. The diagnosis is based on the low haemoglobin, high reticulocyte or nucleated red cell count, and splenic enlargement which is usually 3-6 cm below the costal margin. Treatment is by immediate blood transfusion. The haemoglobin may rise higher than expected because red cells re-enter the circulation from the spleen as it

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Table I: Differential diagnosis of major genotypes of sickle cell disease.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Sickle test</th>
<th>Alkali</th>
<th>Electrophoresis</th>
<th>HbA2 (%)</th>
<th>MCV (fl)</th>
<th>Family studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous sickle cell disease</td>
<td>+</td>
<td>FSA₂</td>
<td>SF</td>
<td>1.5-4.0</td>
<td>80-100</td>
<td>both parents have S gene</td>
</tr>
<tr>
<td>Sickle cell-HbC disease</td>
<td>+</td>
<td>SC</td>
<td>CS</td>
<td>– *</td>
<td>70-90</td>
<td>one parent has HbC gene</td>
</tr>
<tr>
<td>Sickle cell-β⁺ thalassaemia</td>
<td>+</td>
<td>FSA₂</td>
<td>SF</td>
<td>&gt;5.0</td>
<td>60-80</td>
<td>one parent has β⁺ thal gene</td>
</tr>
<tr>
<td>Sickle cell-β⁺⁺ thalassaemia</td>
<td>+</td>
<td>AFSA₂</td>
<td>SAF</td>
<td>&gt;4.0</td>
<td>70-82</td>
<td>one parent has β⁺⁺ thal gene</td>
</tr>
</tbody>
</table>

* HbA₂ levels are not usually measured in SC disease because HbA₂ travels in the same position as HbC.
shrinks. Teaching parents to palpate the spleen daily and bringing the child to the clinic immediately when acute splenic sequestration is suspected has reduced mortality from this complication by 90% in Jamaica. Prophylactic splenectomy usually is recommended after two attacks since events tend to recur at shorter intervals.

The aplastic crisis usually affects children, occurs in epidemics and clusters in families. This condition was observed in 30% of Jamaican Cohort Study children by 15 years [7]. The infection of red cell precursors with human parvovirus [8] causes reticulocytes to disappear from the peripheral blood and the haemoglobin to fall at a rate of approximately 1g/dl/day. This diagnosis is based on anaemia, usually 3-4 g/dl by the time of presentation, and the absence of reticulocytes from the peripheral blood. A daily dramatic increase in the reticulocyte count is consistent with the recovery phase of the aplastic crisis. Treatment is by transfusion. It may be performed as an outpatient with monitoring to ensure recovery of reticulocytosis by bone marrow. This usually occurs after 7-10 days of aplasia. Siblings with SS disease in the same house have a 50% chance of being affected within 3 weeks of the initial aplastic crisis, and should be monitored closely. Immunity appears to be life-long since recurrence of an aplastic crisis has never been described. A human parvovirus vaccine has been developed and is awaiting clinical trial.

**Chronic anaemia**

A gradual lowering of haemoglobin may occur in chronic hypersplenism and may be accompanied by megaloblastic changes in blood cells and by iron deficiency. Sustained, often massive, splenomegaly may be associated with very low haemoglobin concentrations and rapid haemolysis. The aetiology is not well understood but complications associated with superimposed acute splenic sequestration or aplastic crisis, the dangers of thrombocytopenia, and the metabolic demands of a grossly expanded bone marrow often cause other morbidities and occasionally mortality. Growth often ceases but a growth spurt follows splenectomy, presumably because of the greater availability of protein and energy after surgery [9]. Diagnostic criteria are arbitrary. They are based on a sustained and marked splenomegaly (usually 8-15 cm below left costal margin), a low haemoglobin (usually 3-5 g/dl), and a reticulocytosis of 20-30%. Platelet counts are usually reduced (<250×10^9/l) and the red cell survival markedly shortened to 2-3 days. Treatment options include chronic transfusion but splenectomy is preferred in Jamaica if there is no evidence of spontaneous resolution after an observation period of 6 months.

The increased bone marrow activity increases folic acid requirements and deficiency may cause megaloblastic changes, most commonly in the first 3 years. This is particularly common in West Africa [10] where dietary folate is low, but uncommon in sites such as Jamaica where folate supplementation does not improve haematologic indices, clinical features associated with this condition or growth [11]. This diagnosis is based on a gradual fall in haemoglobin level to 2-3 g/dl, low reticulocyte counts of 2-3%, macrocytosis (an increase in MCV of approximately 20 fl and usually exceeding 100 fl) and megaloblasts in the peripheral blood. There is usually a good response to oral folic acid and transfusion is not necessary unless complications such as cardiac failure occur. Local dietary availability of folic acid and the frequency of megaloblastic changes should determine policies on folic acid supplementation (5 mg once or twice weekly).

Iron deficiency may occur from low dietary iron intakes, intestinal infestation or other causes of blood loss. This diagnosis is based on a lowered haemoglobin, low reticulocyte counts, macrocytosis (MCV <75 fl), and biochemical evidence of low serum iron, high unsaturated iron serum binding capacity, or low serum ferritin. Treatment requires rectifying the underlying cause and short term iron supplementation.

Combined iron and folic acid deficiency may cause diagnostic confusion with a hypoplastic picture with low haemoglobin and low reticulocyte count but without change in MCV. There may be biochemical evidence of both iron and folate deficiency and treatment with one agent reveals erythropoiesis limited by the other. Thus treatment with folate reveals iron-limited erythropoiesis (e.g. MCV falls) whereas treatment with iron may...
unmask folate limited erythropoiesis (e.g. MCV rises).

Uncommon in childhood, chronic renal failure may occur as early as adolescence. It is believed to result from a progressive glomerular sclerosis that is consequent to sustained hyperfiltration. This diagnosis is based on a falling haemoglobin level with symptomatic anaemia, a serum creatinine elevated above 60 µmol/l, and low erythropoietin levels. Its treatment requires maintenance of haemoglobin by chronic transfusion or erythropoietin injections. Renal transplantation may be considered.

Gallstones

These form as early as 3-4 years and reached an incidence of 40% in SS patients by the age of 20 years in the Jamaican Cohort Study [12]. Gallstones are usually small and multiple and may cause symptoms by obstructing the cystic duct or common bile duct, or because of acute or chronic cholecystitis. Diagnosis is by ultrasonography. Treatment for asymptomatic gallstones should be conservative although specific symptoms may justify cholecystectomy which may be performed laparoscopically [13].

Fever and infection

The risk of pneumococcal septicaemia is increased greatly and is maximal during the first 3 years of life. Age specific incidence falls sharply after 5 years [14,15]. This diagnosis should be suspected in any seriously sick “septic” child with a high fever and is confirmed by a positive blood culture. Prevention is essential and is achieved by the prophylactic administration of penicillin [14, 16]. This preventive treatment should start at age 4 months and continue until at least 4 years, and should not be stopped without administering pneumococcal vaccine. Penicillin may be given as orally twice daily. To avoid problems with compliance, the Jamaican protocol uses monthly injections of depot penicillin from 4 months to 4 years. Children allergic to penicillin may be given oral erythromycin. The current pneumococcal vaccines do not work well before the age of 3 years but a new conjugated pneumococcal vaccine that may be given at 2, 4, and 6 months is currently under assessment. Penicillin resistant strains of pneumococci are becoming more common.

Septicaemias due to *Haemophilus influenzae* type b [17] and salmonella [18] are also increasingly common. This diagnosis should be suspected in a seriously sick child with high fever, and marked jaundice. Prophylaxis is based on conjugated *H. influenzae* b vaccines. The normal immunisation schedule is between 2-6 months. The frequency of infection and high mortality due to salmonella could also make a case for salmonella prophylaxis pending the results of blood culture. In any febrile, septic child, treatment should consist of broad spectrum antibiotics given intravenously (IV) if possible. A common regime is ceftriaxone (100 mg/kg/d, in two divided doses IV) or, if not available, crystalline penicillin, (100,000-200,000 U/kg/d in a single dose), and chloramphenicol (50-100 mg/kg/d IV, in four divided doses).

Stroke

Stroke affected 8% of the Jamaican Cohort Study by 14 years and occurred at a median age of 8 years [19]. In patients who survive the first stroke, 50-70% develop further episodes within 3 years [20]. The clinical picture consists of a hemiplegia and other pathology associated with infarcts secondary to occlusion of major cerebral vessels. The internal carotid, and anterior or middle cerebral arteries were affected in 71% in one series [21]. Diagnosis is made on the basis of the clinical picture, the extent of cerebral damage that is assessed by magnetic resonance imaging, and the status of cerebral vasculature assessed by angiography or magnetic resonance arteriography. Cerebral haemorrhages into infarcted areas or ruptured aneurysms and subarachnoid haemorrhage also may occur as early as 4 years of age.

Risk factors for initial stroke are largely unknown so prevention is not usually possible. Treatment is based currently on the prevention of recurrent events by chronic transfusion programmes designed to maintain HbS levels below 30%. There are many problems with such programmes. These include alloimmunisation that causes transfusion reactions, iron overload, maintaining
venous access, transfusion acquired infections, and no readily available and effective methods of monitoring. Stroke recurrence in programmes that are successful in maintaining HbS levels fall below 25%. Transfusion reactions continue to occur despite leucocyte and platelet depleted blood and some patients develop enough distinct antibodies as to be untransfusuable. Prevention of iron overload requires chelation with syringe driving pumps that deliver desferrioxamine subcutaneously for at least 5 nights each week. This treatment is expensive and commonly fails in adolescence because of inadequate compliance. Loss of peripheral veins may require permanent ports such as Port-A-Caths or Hickman lines. Transfusion acquired infections have been reduced by screening of transfused blood but a window remains when HIV may be undetectable. Cessation of transfusion programmes after periods of up to 12 years reported stroke recurrence rates that were higher than observed in groups in whom transfusion had never been commenced, resulting in a policy of transfusion for life [22]. The enormous cost and logistical difficulties of this treatment places it beyond the resources of most developing countries. An exchange transfusion, however, may be offered at the acute event and is more feasible in those settings. The high recurrence rate and predictability of further strokes provide a basis for discussing bone marrow transplantation as a potential therapy.

**Bone and abdominal pains**

**Dactylitis (hand-foot syndrome)**
Painful swellings of the small bones of the hands and feet commence as early as 3-4 months, frequently recur, but become rare in groups in whom transfusion had never been commenced, resulting in a policy of transfusion for life [22]. The enormous cost and logistical difficulties of this treatment places it beyond the resources of most developing countries. An exchange transfusion, however, may be offered at the acute event and is more feasible in those settings. The high recurrence rate and predictability of further strokes provide a basis for discussing bone marrow transplantation as a potential therapy.

Infection should be suspected when there is marked swelling over the affected bones, and surgical drainage may be necessary. Treatment of uncomplicated cases requires pain relief and hydration. Parents need reassurance that this manifestation is usually not serious.

**Painful crisis**
The painful crisis is the counterpart of dactylitis in older children and adults. Pain occurs in the juxta-articular areas of the long bones, sternum, spine, and pelvis. Bone pain often commences in childhood and may increase markedly between 15-25 years especially in males [25]. This diagnosis is based on the clinical picture of bone pain, commonly localised tenderness, and is associated often with fever and dark or reddish brown urine. Recognising precipitating factors that include exposure to cooling ambient conditions or events (skin cooling), infection, dehydration, and emotional stress may allow prevention of some painful crises. In Jamaica, cooling of the skin is the most common precipitating event [26]. This results from seasonal changes in temperature, getting caught in rain, taking cold baths especially at colder times of the day, swimming in rivers or the sea, and even limited evaporational cooling that occurs with washing cars or doing laundry. Simple measures such as avoiding cold exposure by bathing at warm times of the day or by heating water may avoid painful crises. Risk factors include pregnancy, the last trimester and early post partum period [27], high total haemoglobin levels and low foetal haemoglobin levels [25, 28].

Treatment consists of reassurance, rest, warmth, hydration, and pain relief. Patients should be taught to keep mild analgesics at home and to take these early in episodes of bone pain. A knowledgeable, confident family can do much to reassure patients and increase coping. Distracting activities such as watching television or playing video games also may reduce the awareness of pain. If simple measures are ineffective, patients should be encouraged to seek medical help early to exclude underlying infections and obtain treatment with stronger analgesics. If the patient is vomiting, dehydrated, or is unable or unwilling to take fluids readily, intravenous fluid is given. In
Jamaica, most cases are monitored in a day care centre and over 90% of those who experience a painful crisis choose to return home to a supportive environment in the evenings.

Abdominal painful crisis
Episodes of abdominal pain are common especially in children and result from a variety of mechanisms. Abdominal pain may be referred from the spine or lower ribs that are affected by avascular necrosis or may be a symptom of the acute chest syndrome especially when this involves the lower lobes. Right upper quadrant or epigastric pain may be associated with symptomatic gallstones although non-specific central abdominal pain is more common in children with gallstones. Usually, however, this pain does not appear to be aetiologically related to the presence of gallstones. A particularly characteristic form of an abdominal painful crisis is one characterized by generalised abdominal pain and distension associated with vomiting and diminished or absent breath sounds. Radiological findings are consistent with ileus, i.e. distended loops of bowel with fluid levels on erect films are observed. The cause of this condition is unknown but in some cases, the clinical picture is consistent with the dysfunction of a localised loop of bowel that may reflect a transient autonomic neuropathy. Although this syndrome may mimic an acute surgical abdomen, treatment should be conservative. Generally treatment with parenteral fluids and naso-oesophageal aspiration results in the restoration of normal gut activity after 2 to 3 days.

Avascular necrosis of the femoral head
This complication occurs most commonly in late adolescence and early adult life although may be seen as early as 8-10 years [29, 30]. The pathological basis is avascular necrosis of the bone marrow. Continued weight bearing on a softened femoral head may lead to damage, irregularity of the joint surface, and a painful limitation of movement. This diagnosis is based on persistent pain on walking that is localised to one hip, and is particularly marked on climbing steps. There may also be a limp. Examination shows painful limitation of passive movement of the affected hip especially on internal or external rotation. Early diagnosis and prevention of further weight bearing may limit destruction of the femoral head. Magnetic resonance imaging is the most sensitive method to diagnose and follow this condition [31, 32]. Observable changes on conventional bone radiology usual signal advanced disease. Treatment should focus on avoidance of weight bearing by alternating plaster casts that maintain flexion of either the hip or the knee for 6 months and the use of crutches. This approach allows the child to remain at school and participate in many normal activities. Occasionally traction in the hospital may be necessary. If permanent damage occurs, limited remodelling surgery may be necessary. Persistent symptoms and functional limitations may require total hip replacement. This, however, rarely is indicated before young adult life.

Acute chest syndrome
This is the biggest single contributor to mortality after the age of 2 years [33] and remains a major cause of morbidity and mortality in SS disease at all ages. The pulmonary pathology includes elements of infection, infarction, embolism and pulmonary sequestration.

The role of infection is controversial. Bacteria were considered frequent causes of infection in children [34] but occurred in only 4 to 14% of children in recent studies [35, 36]. Despite this, it is usual to administer broad spectrum antibiotics to prevent secondary infection of infarcted areas. Clinical presentations are similar to those seen in patients with pneumonia, fever, cough, dyspnoea and pleuritic pain. These signs and symptoms do not usually resolve promptly with antibiotic therapy but run complicated clinical courses.

Fat embolisms may occur secondary to bone marrow infarction and generally manifest a severe progressive course. In the past, this diagnosis was confined to autopsy when fat globules, necrotic bone marrow and even spicules of bone were seen in pulmonary capillaries [37]. Currently this diagnosis may be made in vivo when fat-laden pulmonary macrophages are detected. These were reported in the bronchoalveolar fluid of 12/27 patients with acute chest syndrome in the Cooperative Study of Sickle Cell Disease [38]. The clinical course commences with a typical bone pain crisis.
The clinical condition usually deteriorates. Severe back pain, chest tightness, dyspnoea, falling arterial oxygen tension and signs of systemic embolism (respiratory, renal, and cerebral involvement and occasionally skin petechiae) follow. There is often laboratory evidence of disseminated intravascular coagulation. Treatment includes exchange transfusions, antibiotics, oxygen, and/or heparin.

Stasis in the pulmonary capillaries impairs gas exchange promoting a vicious cycle of deoxygenation, sickling, and further stasis. Patients deteriorate rapidly with extensive radiological lung opacities (“white-out”) and progressive dyspnoea. This is a life threatening emergency that may respond to emergency exchange transfusions, repeated after 4-6 hours. In successful cases, dyspnoea and radiological pulmonary white-out may be reversed within 48 hours indicating that this condition is due to an acutely reversible vascular pathology. Because of the rapid deterioration that may occur in patients with the acute chest syndrome, it is good clinical practice to monitor all severe cases by pulse oximetry and to use emergency exchange transfusions early if rapid deterioration occurs [39-41].

Avascular necrosis of the ribs or sternum also may cause a pleuritic type of pain with respiratory movements. This condition is diagnosed by localised tenderness and sometimes swelling of the affected bones [42]. The lungs initially are unaffected clinically, although lung involvement may develop secondary to splinting and reduced movement of the affected ribs. Incentive spirometry in patients with rib necrosis significantly reduces the risk of secondary acute chest syndrome [43].

**Eyes**

Vaso-occlusion of the peripheral retina precedes the development of proliferative sickle retinopathy. This condition may cause vitreous haemorrhage and transient blurring of vision or rarely retinal detachment and permanent visual loss. These occur most commonly in late adolescence and early adult life. Proliferative sickle retinopathy occurs predominantly in the relatively benign syndromes, SC disease and sickle cell-β+ thalassemia. Annual ocular assessments in the Jamaican Cohort Study detected retinopathy as early as 8 years. The greatest incidence was noted in late adolescence. These lesions may be rendered avascular by either coagulation of the feeding arterioles [44]. Treatment with an xenon arc or argon laser may also result in an ischaemic retina [45] but spontaneous non-perfusion (auto-infarction) is also common. Visual loss is relatively uncommon and until the risk factors for auto-infarction and the natural history of sickle cell eye disease are better understood, it is probably better to avoid photocoagulation therapy, especially in children.

**Genito-urinary problems**

**Priapism**

Involuntary painful erection of the penis affects approximately 30-40% of postpubertal Jamaican male patients with SS disease [46] and also may occur in early adolescence. There are two clinical patterns, stuttering priapism which is generally nocturnal, lasts 3-4 hours, is relieved by simple physical measures such as exercise, and does not impair normal sexual function, and major attacks lasting >24 hours, with extreme pain, often penile oedema, and usually followed by irreversible damage to the vascular erectile system and impotence. Stuttering attacks are commonly a prodrome for a major attack although some major attacks occur de novo. Stuttering attacks may be relieved by stilboestrol [47] or by injections of luteinizing hormone releasing hormone (LHRH). This latter treatment has not been tested in controlled trials. Major attacks generally require surgical relief. These should be minimal, such as aspiration and irrigation of the corpora by wide bore needles or a spongioso-cavernosal shunt. Although major attacks commonly result in impotence in adults, the outlook appears to be more benign in children.

**Enuresis**

Nocturnal enuresis, defined as bed wetting at least 2 nights weekly, occurred in 52% boys and 38% girls by age 8 years in the Jamaican Cohort Study [48]. The aetiology mechanism for this condition may be related to high urinary volumes and lower functional bladder capacities [49]. Treatment is unsatisfactory. It relies on conservative measures such as limiting late fluid intake and waking the
child to empty the bladder during the night. Enuresis alarms may help but enuresis always eventually resolves spontaneously.

Renal disease
Renal tubular damage that impairs the ability to concentrate urine from early childhood is common in SS disease. High glomerular filtration rates occur in childhood and are believed to predispose to the progressive glomerular damage and glomerulosclerosis that are common in older adults. Renal failure is predominantly a problem of later adult life but may occasionally occur in adolescence. Symptoms of renal disease usually result from low haemoglobin concentrations that are secondary to reduced erythropoietin production. It may be treated by top-up transfusions, recombinant human erythropoietin, or in severe cases renal transplantation.

Leg ulcers
Chronic leg ulcers around the ankles affect 75% of Jamaican SS adults although are less common in Europe and the USA [50, 51]. They develop most frequently between the ages of 15-20 years at a critical time for education. There is a direct relationship between age at ulceration and educational attainment. Healing is generally slow and ulcers are prone to relapse spontaneously. Treatment includes debridement with proteolytic enzymes or crushed papaya in Jamaica, regular dressing at home twice daily with mild antiseptic agents. There is no reliable response to topical or systemic antibiotics although some patients show marked benefit once the ulcer is clean. Oral zinc sulphate (200 mg three times daily) significantly improved healing in a controlled trial [52]. Skin grafting (pinch grafts) may be used in clean vascular ulcers but walking before complete healing commonly leads to failure of the pinch grafts. Complete bed rest always improves ulcer healing and there is no evidence for a beneficial effect of transfusion or hyperbaric oxygen.

Growth
A low weight gain in the first year of life, decreased body fat, and thinner skin folds are characteristic of SS patients throughout life [53, 54]. Height also lags behind by the first year. Height/length deficits increase yearly especially at ages when normal children enter the puberty associated growth spurt. Puberty in SS disease is delayed. Its onset, however, is associated with increased height velocity, and the final height is similar or exceeds that of the normal population. It is important to explain these growth differences to parents, so that they are reassured and avoid spending resources on diverse treatments to promote growth.

Pregnancy and contraception
Sexual development is retarded. A mean delay of menarche in girls of 2.5 years was observed in the Jamaican Cohort Study but the interval between the first unprotected sexual exposure and pregnancy is similar in SS disease and normal controls [55]. Painful crises and the acute chest syndrome are increased especially in the third trimester of pregnancy and in the immediate post partum period. There is a 1% maternal mortality associated with pregnancy in Jamaica. Foetal loss is increased at every stage of pregnancy and infants are usually of low birth weight. All mothers should receive regular antenatal care with daily supplementation by iron and folic acid. All deliveries of SS patients should be in hospital. There is no evidence that prophylactic transfusions improve foetal outcome. This is not performed in Jamaican management of pregnancy.

Patients requesting contraception should be given the best methods available. Although the risks of pregnancy are small, they far outweigh any theoretical risks of contraception. The injectable contraceptive medroxyprogesterone (Depopovera®) has the advantage of increasing red cell survival and decreasing bone pain in SS disease [56], and is the method of choice. Many Jamaican patients prefer to have regular menstruation and choose the low estrogen pill. An intra-uterine device is offered to patients requesting longer lasting methods or tubal ligation if sterilization is desired.

Surgery and anesthesia
Conservative management is preferred for asymptomatic gallstones and non specific abdominal pain. Common causes of surgery include splenec-
tomy, orthopedic procedures, and childhood operations incidental to sickle cell disease such as tonsillectomy and adenoidectomy. Elective surgeries should be performed only when the patient is clinically well and at steady state haemoglobin levels. Preoperative transfusions are not routine in Jamaica but blood is cross-matched to replace any blood lost at surgery [57]. Most patients are preoxygenated before induction and close monitoring is essential in the immediate postoperative period when anaesthesia-induced respiratory depression is common. Continued oxygenation and physiotherapy is important following upper abdominal surgery to prevent postoperative acute chest syndrome. Preoperative transfusion is used widely elsewhere. A randomised study in the Cooperative Study in the USA found, however, no difference between preoperative simple and aggressive transfusion regimes [58]. Jamaican experience without transfusion has a similar morbidity to that observed in transfused groups elsewhere casting doubt on the value of routine preoperative transfusions.

Diagnosis and counseling

Early diagnosis is essential in order to implement education and preventive programmes designed to reduce the early morbidity and mortality of SS disease. Analysis of DNA isolated from amniotic fluid or chorionic villi can detect the presence of the SS genotype in a foetus at 12-14 weeks of gestation [59, 60]. Early diagnosis offers parents the option of terminating an affected pregnancy, but the inability to predict the clinical course of the child deprives the parents of vital information in this decision. Parents who already have a child with sickle cell disease and therefore have enough information for self-counselling are more likely to act on this information.

Diagnosis screening at birth is simple, cost effective and should be implemented in all communities [61]. Only then can penicillin prophylaxis, parental education of acute splenic sequestration, complete immunization, better management of aplastic crises, and general education on disease management have full potential impact in improving survival from the disease. Counseling services should explain the basic genetics of the disease and the chances of producing affected children in the future. Prenatal diagnosis should be available for couples who wish to make informed decisions on whether or not to complete an affected pregnancy. Social and general support services can help patients and their families find solutions to social and other problems, which often accompany symptoms of the disease.

New approaches to treatment

There have been many attempts to find effective antisickling agents on the assumption that inhibiting sickling may ameliorate manifestations of the disease. Inducing higher levels of foetal haemoglobin has been achieved by hydroxyurea. This has resulted in significant reductions in the prevalence of painful crises and in transfusion requirements in a selected group of severely affected adults [62]. Chronic transfusion programmes have been over utilized and although they may provide short-term benefits, they often induce serious iatrogenic pathology. In Jamaica, very few patients receive regular transfusion. The only recipients are a small group with chronic renal failure and no patients currently receive hydroxyurea for the prevention of painful crises. Other more appropriate approaches appear for preventing and managing painful crises. Because a high haemoglobin is a clearly documented risk factor [26, 28], venesection is currently under controlled assessment. Available knowledge of the disease’s natural history is not detailed sufficiently to predict the most appropriate forms of intervention. Bone marrow transplantation may represent a treatment option to prevent stroke recurrence. However, cost, short-term mortality of 10%, limited availability of suitable compatible donors, and long-term risks of sterility mandate a cautious approach [63].

Care is best provided in specialised centers with extensive experience in managing the disease successfully and with competent staff in whom the patient has confidence. Patients should be reviewed regularly at 3-6 month intervals when clinically well and encouraged to seek treatment at any time if sick. Steady state haematological assessments are performed in Jamaica every 2 years or
more frequently if clinically indicated and these allow earlier detection of problems such as chronic renal failure. Counselling and other support services should be available within the center. A day care approach to the management of painful crises may provide a more acceptable alternative to frequent emergency room attendance or hospital admissions. The first 5 years hold the greatest risk of mortality for patients with sickle cell disease and prevention or more effective management of common complications can improve survival significantly [64]. Currently average survival of patients with SS disease in the USA is approximately 50 years. Longevity will continue to improve with better medical and social care.

Conclusion

Although the disease currently cannot be cured, many of its complications can be prevented or more effectively treated if the underlying disease is detected. The optimal treatment of sickle cell disease is based on early diagnosis, preferably by newborn screening, and close follow-up in centres with special knowledge and expertise in sickle cell disease. The management of sickle cell disease has improved markedly in the last 30 years and average survival of patients with SS disease is now approaching 50 years. Paediatricians have an essential role to play in reducing morbidity and mortality and promoting survival to adult life.

References


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