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Sickle cell disease; a general overview

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ABSTRACT

Sickle cell disease (SCD) is a heterogeneous disorder, with clinical manifestations including chronic haemolysis, an increased susceptibility to infections and vaso-occlusive complications often requiring medical care. Patients with SCD can develop specific and sometimes life-threatening complications, as well as extensive organ damage reducing both their quality of life and their life expectancy. Proven effective treatment options for sickle cell patients are limited to hydroxyurea, blood transfusions and bone marrow transplantation. With the increasing prevalence of SCD in the Netherlands, a fundamental understanding of its pathophysiology and clinical syndromes is of importance for local medical practitioners.

INTRODUCTION

Sickle cell disease (SCD) is clinically one of the most important haemoglobinopathies. It is characterised by haemolytic anaemia, an increased susceptibility to infections and vaso-occlusion that occurs in almost all vascular beds leading to ischaemic tissue injury with organ dysfunction and early death. Outcome is difficult to predict, and few effective therapeutics are available. The prevalence of SCD is on the rise in the Netherlands due to an increased immigration of people from Surinam, the Netherlands Antilles and African countries.[1] A recent survey (with only a 30% response) covering more than 400 Dutch hospital departments where patients with haemoglobinopathies could be registered indicated a population of at least 450 SCD patients (PC Giordano, manuscript in preparation). This implies that the treatment of sickle cell patients will increasingly be required from general practitioners, internists and haematologists in the Netherlands. Therefore, a fundamental understanding and knowledge of the clinical syndromes of sickle cell patients is of importance for those practicing medicine in the Netherlands. Education of both patients and their families about SCD is also of importance, and the efforts of patient organisations such as the OSCAR (Organisation for Sickle Cell Anaemia Relief; www.sikkelcel.nl) are contributing significantly to the increased awareness of haemoglobinopathies in the Netherlands. This review is not intended to provide specific management guidelines (as can be found in the referenced textbooks and specific papers), but to provide a general overview of some of its major complications and some of the current problems with regard to its general management.

NORMAL HAEMOGLOBIN AND SICKLE HAEMOGLOBIN

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 ($\alpha_2\beta_2$). Other haemoglobins are HbA_2 (2 to 3.5%; $\alpha_2\delta_2$) and HbF (<2%; $\alpha_2\gamma_2$). During intrauterine development, several globin chains are synthesised (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 HbA_2 as the remaining haemoglobins.[2] The β globin gene is found on chromosome 11p15.5. A single point mutation in the 6th codon leads to substitution of glutamic acid for valine, resulting in an abnormal globin: β^S. This results in the formation of 'sickle haemoglobin', or HbS ($\alpha_2\beta^S_2$). Upon deoxygenation, β^S forms hydrophobic interactions with adjacent β^S globins, ultimately resulting in the polymerisation of HbS. This is the molecular hallmark of SCD.[3] As a consequence, the normally pliable RBC assumes a rigid sickled shape, with ensuing erythrocyte membrane damage and haemolysis. James Herrick, a cardiologist in Chicago, described the first case of SCD in Western literature in 1910.[4] He was alerted by his intern, Ernest E. Irons, about an anaemic black man coping with respiratory problems in whom he noted 'peculiar elongated and sickle shaped' RBC's on a blood smear. The patient was a dental student from Grenada named Walter Clement Noel. After becoming a dentist and practicing shortly in Grenada, Noel died of pneumonia, or possibly an acute chest syndrome (ACS).[5] In the last decades a wealth of information has been produced regarding the potential mechanisms by which the simple β^S mutation leads to the protean clinical manifestations of SCD.

The largest proportion of SCD occurs among blacks, both in Africa and in countries with slave trading histories. In several areas in Africa and in Asia the β^S gene has arisen independently as a new mutation. Recognised by differences in the β globin gene cluster, these haplotypes are named after the areas where they were first described (Senegal, Bantu, Benin, Cameroon and Arab/Indian haplotypes).[6] Inheritance of two β^S genes leads to homozygous SCD, or sickle cell anaemia (HbSS). Other genotypes that give rise to SCD include double heterozygous states in which the β^S gene is inherited together with other abnormal β genes, or with mutations that result in decreased synthesis of β globin genes (β-thalassaemias). In HbC a mutation in the β gene results in substitution of glutamic acid by lysine. The HbSC genotype is the most common double heterozygous state, followed by HbSβ-thalassaemia.[7] People who carry just one β^S mutation have the sickle cell trait (HbAS), and are generally asymptomatic.[8] Hence, the disease is recessive with respect to clinical manifestations, but the gene is dominant in its expression since sickled cells can always be visualised in deoxygenated blood of individuals with HbAS. Combinations of HbAS with β-thalassaemias and of HbSS (or other forms of SCD) with α-thalassaemias (mutations that result in decreased synthesis of α globin genes) give rise to SCD with varying severity depending on the number and type of gene deletions.[7] The survival advantage of people with sickle cell trait with regard to infections with *Plasmodium falciparum* may explain the association of malaria distribution and the distribution of the sickle cell gene, as well as the balanced polymorphism of the β^S gene in the African population.[9,10] In some parts of Africa 45% of the population is heterozygous for the β^S gene and in the United States and the Caribbean about 8% of blacks carry one β^S gene. The β^S gene also occurs in the Caribbean, the Mediterranean basin, Saudi Arabia and in parts of India.[11]

DETERMINANTS OF HbS POLYMERISATION

The pathophysiological hallmark of SCD is intracellular polymerisation of HbS upon deoxygenation.[3] Decrements in pH (which reduce the affinity of haemoglobin for oxygen) enhance HbS polymerisation, as does a rise in temperature.[12] The concentration of HbS in the erythrocytes is also of great importance, with higher concentrations of HbS leading to more rapid polymerisation. Another determinant of the tendency for polymerisation is the presence of other haemoglobins, with HbF and HbA_2 limiting the HbS polymerisation to a greater extent than HbC and HbA. HbSS patients have no HbA, an HbS% greater than 85%, a normal HbA_2% and an elevated HbF%. In people with HbAS, the HbS% is approximately 40%. In HbSC patients the HbS% is about 10 to 15% higher and the mean corpuscular haemoglobin concentration (MCHC) is elevated (due to HbC-induced erythrocyte potassium and water loss), explaining why people with HbSC can be severely affected (as opposed to the largely asymptomatic people with sickle cell trait).[13,14] HbS polymerises effectively with other less common haemoglobin variants such as HbD-$^{\text{Los Angeles}}$ and HbO-$^{\text{Arab}}$ leading to less frequent double heterozygous forms of SCD.[7] In combinations of HbS and β°-thalassaemia (no β globin synthesis from the affected thalassaemic allele), there is no normal β globin production and hence no HbA. These patients show an HbS% similar to that of HbSS patients (>85%). Inheritance of HbS with β^+-thalassaemia (reduced β globin synthesis from the affected thalassaemic allele) leads to a variable HbA% (ranging from 1 to 25%), and hence, a variable HbS%.[7] Combinations of HbSS with α-thalassaemia lead to a slight elevation of the HbA_2% with a concomitant reduction of the HbS%. In patients with HbSβ-thalassaemias and HbSS with α-thalassaemia the mean corpuscular volume (MCV) and the MCHC are reduced, thereby lowering the HbS polymerisation rate as compared to HbSS patients.[6]

CLINICAL MANIFESTATIONS

Sickled erythrocytes get entrapped in the microcirculation, thereby causing ischaemic organ damage throughout the body. For haemoglobin to polymerise in the microcirculation the HbS% and concentration should be sufficiently

high so that the delay time (Td: the time needed for HbS to form rigid polymers) is shorter than the transit time (Tt: the time needed for erythrocytes to traverse the microcirculation).[3] In the last decades it has become clear that adhesive interactions between activated vascular endothelial cells, erythrocytes, leucocytes and platelets lead to an increased Tt, thereby contributing to the vaso-occlusive process.[15] Also, a proinflammatory state, hypercoagulability and endothelial dysfunction contribute to sickle cell vaso-occlusion.[16-18] If sickled erythrocytes escape the microcirculation, the HbS polymer becomes soluble again after reoxygenation and the red cell can reassume its biconcave shape. However, with repetitive sickling and un-sickling cycles, dense irreversibly sickled cells (ISCs) are formed that are characterised by a significantly reduced lifespan as compared with non-ISCs.[19] From a clinical viewpoint, disease manifestations can be roughly attributed to two phenomena: haemolysis and vaso-occlusion.

Haemolysis

Haemolytic anaemia occurs in all significant forms of SCD, but is less severe in patients with concomitant thalassaemia, HbSC, and/or a high HbF%.[14,20] Red cell survival is estimated to be about 17 days in HbSS patients, which is in striking contrast to the 120 days in healthy persons.[19] Intravascular haemolysis in SCD results from complement recognition of sickling-induced membrane changes, cell dehydration and direct membrane damage by rigid haemoglobin polymers.[19] Monocyte and macrophage destruction of physically entrapped cells in the microcirculation also contributes to the shortened erythrocyte lifespan.[21] While there is a great variability between patients, following the decline of the HbF% after birth, the haemoglobin level (and both the haemolytic rate and number of ISCs) remains relatively constant until about 40 years of age. After the fourth decade, haemoglobin levels fall, possibly as the result of declining renal function and marrow failure due to scarring and fibrosis.[19,22,23]

The consequences of haemolytic anaemia in SCD are diverse. In order to compensate for the reduced oxygen-carrying capacity, sickle cell patients have a hyperdynamic circulation, an expanded plasma volume, and develop dilated cardiomyopathy at an early age.[24] As the affinity of HbS for oxygen is decreased in comparison with HbA, tissue oxygenation may be relatively preserved (in absence of vaso-occlusion), hence explaining the rather good tolerance of anaemia in this patient group.[8] Due to the increased erythropoiesis, bone marrow sites that normally become inactivated shortly after birth (such as the skull and femura) remain active.[8] As result of the chronic haemolysis there are increased levels of unconjugated bilirubin, leading to jaundice and a high incidence of pigmented gallstones. Even though these do not usually require surgical removal, laparoscopic cholecystectomy is the most common elective surgical procedure in SCD.[25-27] Infections with human *parvovirus B19* can lead to life-threatening aplastic anaemia in sickle cell patients.[28]

Vaso-occlusion

Entrapment of sickled cells in the microcirculation leads to tissue ischaemia and damage in almost all organs. This vaso-occlusive process accounts for the majority of SCD-related complications and the affected vascular bed determines its clinical presentation.

The most frequent cause of hospitalisation in sickle cell patients is the *painful crisis*.[29-31] Microvascular occlusion of the bone marrow leads to tissue ischaemia with often excruciating pain necessitating hospital admission and treatment with opioid analgesics. Pain is often located in the lumbar spine, femura, ribs, and sternum. Pain is also often located in the abdomen. The aetiology of 'abdominal crises' is not clear. It is diagnosed by ruling out other obvious causes of intra-abdominal pathology. An abdominal crisis can be associated with bowel distension and/or clinical ileus, and may be mistaken for an acute abdominal problem requiring surgical intervention such as appendicitis. Conversely, it has been suggested that appendicitis in SCD is associated with a higher frequency of transmural necrosis due to vaso-occlusion in inflamed tissue.[32,33] Therefore, the threshold for performing abdominal imaging studies in sickle cell patients with abdominal pain should be low. Fever is common during painful crises often without documentation of infection and it mostly resolves without antibiotics. Painful crises may be precipitated by skin cooling, dehydration, infection, or emotional stress, but mostly no specific cause can be identified.[34] Painful crises occur with increased frequency in pregnant women.[34-36] Patients who experience painful crises more often than three times a year have a shorter life expectancy as opposed to those who experience less than three painful crises per year.[30] 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 (*figure 1*).[34] Although not usually life-threatening, painful crises have been associated with sudden death, and can sometimes be followed by an acute multiorgan failure syndrome characterised by worsening of haemolysis, a drop in platelet counts, often encephalopathy and the failure of at least two major organs.[37-39] Pain has a major impact on the quality of life in sickle cell patients, which is underestimated by solely regarding those painful events that require medical care.[40,41] Patients with higher haemoglobin levels (as occurs in patients with concomitant α-thalassaemia) and lower HbF% are admitted more often for treatment of painful crises.[30,35]

A frequent cause of hospitalisation and a leading cause of death is the *acute chest syndrome (ACS)*, which is a clinical syndrome characterised by a new pulmonary infiltrate on

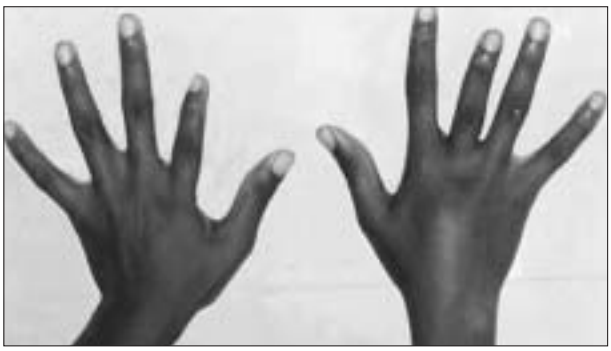

Figure 1
Shortened digits

Shortened left index finger and right middle finger in a sickle cell patient as a result of a hand-foot syndrome (kindly provided by Professor G.R. Serjeant).

chest X-ray in a patient with either dyspnoea, pleuritic pain, cough or fever and often a fall in the haemoglobin level (*figure 2*).[31,37,42-44] Importantly, it can initially present with a normal chest X-ray or solely with perfusion defects on a lung radioisotope scan. The ACS occurs in 15 to 40% of patients, and often recurs. The aetiology comprises a spectrum of sequestration of sickled cells, fat embolism and thrombosis in the pulmonary vasculature.[43-45] The differentiation of an ACS from pneumonia (which also occurs frequently) is difficult in a sickle cell patient with respiratory symptoms. High fever and purulent sputum favour the diagnosis of pneumonia, whereas worsening of symptoms with progressive hypoxia (despite oxygen supplementation and antibiotic treatment) with multilobe involvement is highly suggestive of ACS. ACSs are often preceded by painful crises, but painful crises can also occur secondarily to pneumonia (as can ACSs). In a recent landmark study, infectious pathogens were identified in approximately 29% of cases.[44] Atypical micro-organisms such as *Chlamydia pneumoniae* were often involved, as were common bacterial and viral airway pathogens.[44] Risk factors for ACSs are previous ACSs, elevated baseline leucocyte counts and lower HbF%, whereas lower haemoglobin levels are associated with a decreased risk for ACSs.[46] Chronic sickle lung disease, characterised by dyspnoea with both obstructive and restrictive lung disease, as well as by pulmonary hypertension with cor pulmonale, occurs in patients with previous ACS and may be related to extensive fibrosis due to vaso-occlusive injury as well as to *in situ* pulmonary arterial thrombosis (*figure 3*).[39,47-49] Overt *stroke* occurs in up to 11% of patients with SCD before the third decade of life, and is one of its most devastating complications and a leading cause of death.[31,37,50,51] The highest incidence is observed in the first decade of life, with a high recurrence rate.[52,53] Both ischaemic and haemorrhagic stroke occur at all ages, even though ischaemic stroke occurs more frequently in the young, and haemorrhagic stroke is more frequent in patients in the third decade of life.[37,39,52] Occlusion of large vessels due to thrombus formation on narrowed lumina as result of intima hyperplasia is a factor of major importance in the pathogenesis of ischaemic stroke.[54] Cerebral venous thrombosis is also described.[55] Intracranial haemorrhage may be subarachnoid, intraventricular or parenchymal. Risk factors for stroke include low haemoglobin levels, elevated leucocyte

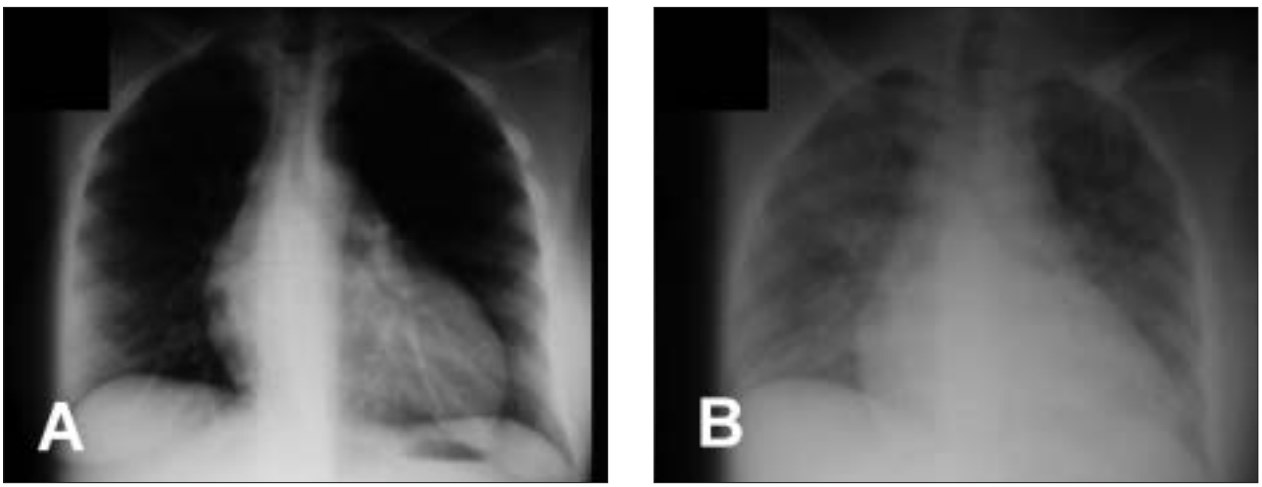

Figure 2
Pulmonary manifestations

Chest X-ray (A) of an 18-year-old HbSS patient during the clinically asymptomatic state. Note the cardiomegaly. Chest X-ray (B) of the same patient several weeks later. During a painful crisis, she developed rapidly progressive respiratory failure with low-grade fever, worsening of haemolysis and chest pain. She refused blood transfusions because of religious beliefs. She died several days later from this episode of acute chest syndrome. No infectious pathogens were identified.

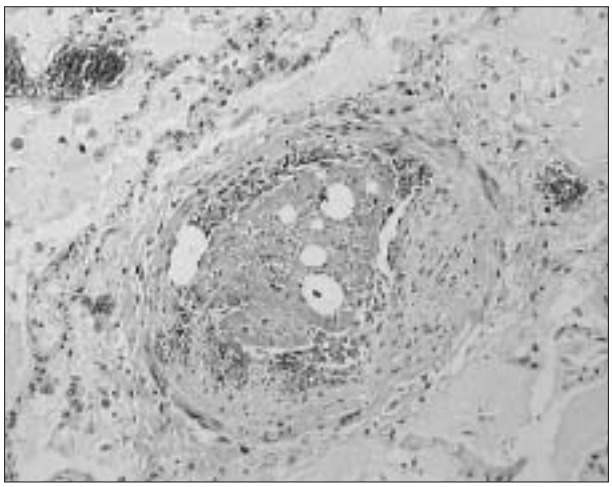

Figure 3
Pulmonary thrombotic arteriopathy

Organising thrombosis in a small pulmonary artery with recanalisation and reactive intimal proliferation in a 37-year-old HbSC patient who died of bacterial sepsis. Such lesions were widespread throughout the lungs.

counts, dactylitis in infants, nocturnal hypoxaemia, a low HbF% and possibly elevated homocysteine levels.[52,56-58] Recent ACSs, as well as frequent ACSs, are risk factors for stroke, as is systolic hypertension.[59,60] The presence of Moyamoya collateral vessels confers a high risk for stroke recurrence, and the increased incidence of stroke in siblings of sickle cell patients with stroke is suggestive of genetic susceptibility within a SCD genotype.[61,62] A marginal protective effect of α-thalassaemia has been reported against both stroke and cerebral vascular abnormalities.[52,63] Cognitive impairment has been associated with ischaemic brain lesions in absence of clinically overt stroke.[64] This silent brain disease may occur in up to a third of SCD patients screened with magnetic resonance imaging and is associated with an increased risk of overt stroke.[65] Central nervous system vasculopathy may be seen in as many as half of the paediatric HbSS patients without clinically overt stroke.[66,67]

Renal dysfunction occurs to some degree in most forms of SCD being a leading cause of death beyond the fourth decade.[37] Due to the extreme interstitial hypertonicity, acidic environment and low oxygen tension of the renal medulla, vaso-occlusion readily occurs in the vasa recta of the kidneys in sickle cell patients and even in subjects with sickle cell trait.[68] This leads to a reduced urine concentrating capacity predisposing patients to dehydration and subsequent vaso-occlusive complications. Patients may suffer from enuresis nocturna. Glomerular injury is common, and may be the result of increased renal blood flow due to the expanded plasma volume and hyperdynamic circulation.[68,69] Severe renal impairment occurs in 4 to 18% of HbSS adults and is often preceded by progressive proteinuria.[70] An incomplete form of distal tubular acidosis is frequently encountered.

The spleen is one of the first organs to be affected in SCD.[71] Blood flow through splenic sinusoids is sluggish, while oxygen tension and pH are low, all favouring the sickling process. In the majority of HbSS infants, a period of hypersplenism is followed by splenic atrophy and loss of splenic function due to vaso-occlusive auto-infarction, whereas splenomegaly (with or without hyposplenism) persists in patients with a high HbF% and in double heterozygous states.[71] *Hyposplenism* renders patients susceptible to overwhelming infections with encapsulated micro-organisms such as *Streptococcus pneumoniae*.[72] Indeed, bacterial infections (pneumonia and meningitis) are still a major cause of death in paediatric patients and pose an important problem in adults as well.[29,39,51] Before splenic atrophy occurs, pooling of blood may lead to severe anaemia and failure to thrive. *Acute splenic sequestration* of blood with life-threatening anaemia is a serious complication with a high mortality rate which occurs before splenic atrophy takes place.[71] Patients in whom the spleen remains anatomically intact remain at risk of this complication. The syndrome presents with massive painful splenomegaly, severe anaemia and cardiovascular collapse.

Painful *skin ulceration* around the ankles is common in patients with homozygous SCD with a peak incidence during the second and third decades of life (*figure 4*).[73] Even though vaso-occlusion contributes significantly to the poor healing tendency, it is probably not the sole aetiological event as it occurs in other haemolytic anaemias as well. Its pathogenesis has not been elucidated. Up to 75% of adult HbSS patients will experience this complication and it also occurs in double heterozygous sickle cell patients.[31]

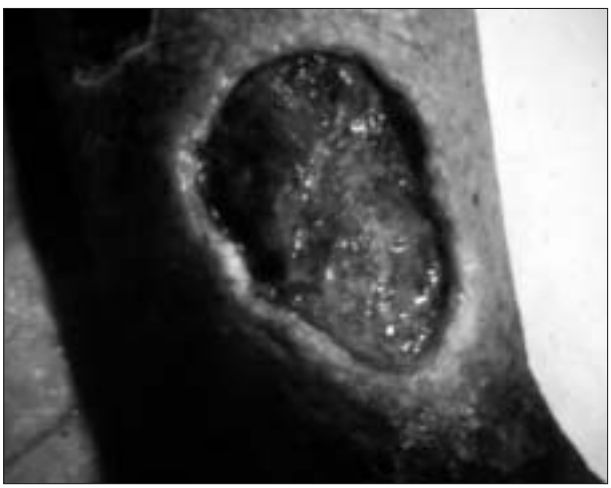

Figure 4
Leg ulcer

Painful nonhealing leg ulcer on the lateral malleolus of a 35-year-old male HbSS patient.

It occurs more often in males, patients with a low HbF%, and with low haemoglobin levels. Alpha-thalassaemia may be protective for the development of skin ulceration.[73-75] Other important complications related to vaso-occlusion that occur in most forms of SCD include priapism and avascular necrosis mostly of the femoral head.[75] Possibly, myocardial infarction occurs due to obstruction of the coronary vasculature by sickled cells in absence of atherosclerosis.[76-79] Sickle retinopathy is the result of vaso-occlusion in the peripheral retina and is a common complication especially in HbSC patients.[31,80] In order to shunt blood beyond ischaemic retinal areas, progressive neovascularisation and enlargement of pre-existing capillaries occurs. Vitreous haemorrhage is a common complication and may result in blindness. Hyphaema, even when it occurs in people with HbAS, can lead to sudden blindness due to compromised blood circulation with increased intraocular pressure as a result of entrapment of sickled erythrocytes in the outflow apparatus of the anterior chamber.[80] Vaso-occlusion in cochlear structures can result in hearing loss.[81,82] Of the infectious complications, osteomyelitis occurs frequently, especially from *Salmonella*.[11]

DIAGNOSIS

The diagnosis SCD should be suspected in patients presenting with haemolytic anaemia or any of the clinical syndromes described above. Importantly, SCD is not solely confined to individuals of African descent.[83] Haemolytic anaemia, characterised by low haemoglobin levels, reticulocytosis, elevated serum levels of lactate dehydrogenase and low serum haptoglobin levels, is present in all major forms of SCD. The MCV is normal to slightly elevated, while a reduced MCV is indicative of either concurring thalassaemia or iron deficiency. Visualisation of sickled red cells on a routine peripheral blood smear is not seen in sickle cell trait (unless there is severe hypoxia), thus indicating SCD. The presence of Howell-Jolly bodies reflects loss of splenic function.[84] The haemoglobin solubility test can be employed as a rapid screening test for the presence of HbS, but it does not distinguish between the different genotypes. It is based on the demonstration of a haemoglobin precipitate following oxygen extraction. Haemoglobin electrophoresis, high performance liquid chromatography and iso-electric focusing can be used to determine the presence of abnormal haemoglobins. The presence of HbS with an elevated HbF% and absence of HbA indicates either HbSS or HbSβ°-thalassaemia. Patients with HbSβ°-thalassaemia are normally characterised by a reduced MCV, and have a (mildly) elevated HbA_2%. In contrast, HbSS patients usually have an MCV and HbA_2% in the normal range. Combinations of HbSS with α-thalassaemia can lead to microcytosis with similar haemoglobin patterns as in HbSβ°-thalassaemia. Distinguishing between such genotypes requires family or DNA-based studies such as PCR analysis of known mutations using well defined primers and SSCP (single-strand conformation polymorphism) for unknown mutations. A high HbA% with an HbS fraction above 50% indicates HbSβ$^+$-thalassaemia. In sickle cell trait the HbS% is below 50, but an HbS fraction lower than 35 to 40% is indicative of concurrent α-thalassaemia. The diagnosis HbSC is straightforward, as both HbS and HbC are demonstrated.[84] Importantly, the clinician should realise that recent blood transfusions can result in an erroneous diagnosis.

MANAGEMENT

The management of SCD begins by informing couples at high risk of conceiving children with SCD about the possibilities of prenatal diagnostic testing. Early detection of patients with SCD by newborn screening programmes enables early provision of comprehensive care, which in itself will improve the quality of life and survival of this patient population.[83,85-87] All clinicians caring for patients with SCD should bear in mind that the extent of damage to vital organs is greatly underestimated if one solely relies on clinical manifestations, as was elegantly demonstrated in a landmark autopsy study.[39]

Vaccination against *Streptococcus pneumoniae* (and *Haemophilus influenzae*), as well as penicillin prophylaxis during childhood, have dramatically reduced infection-related mortality in both the USA and Jamaica.[11,87-89] By instructing parents to rapidly seek medical attention when the spleen enlarges and/or with increasing pallor of the skin, the mortality due to splenic sequestration crises and aplastic crises has been significantly reduced in children with SCD.[27,88]

Clinical management of painful crisis encompasses rapid pain relief, fluid administration to correct and prevent dehydration, treatment of a potential underlying infection, oxygen supplementation if indicated, and incentive spirometry in patients with thoracic pain to prevent ACSs.[90-92] Managing sickle cell patients with respiratory symptoms can be challenging, as the differentiation between pneumonia and the ACS can be very difficult. A general management strategy could be to treat all patients presenting with a new pulmonary infiltrate with antibiotics (covering common respiratory tract pathogens as well as micro-organisms such as *Chlamydia* and *Mycoplasma pneumoniae*) and supplemental oxygen. With deterioration of the patient's condition or progression of pulmonary infiltrates the diagnosis is more likely an ACS and blood (exchange) transfusions should be immediately instituted.[42,44,93] There are no data regarding the role of anticoagulation in the management of an ACS, but with documentation of thromboembolism anticoagulation is warranted.

Even though it does not reduce the incidence of acute vaso-occlusive events that require medical care, folate is often prescribed to prevent megaloblastic erythropoiesis.[94] It may be advisable to prescribe folate to all sickle cell patients to reduce at least one easily avoidable potential risk factor for complications by keeping homocysteine levels as low as possible.[56,95] Based upon several clinical observations, it has been suggested that iron deficiency may ameliorate SCD-related symptoms due to lowering of the MCHC. Therefore, worsening of symptoms upon repletion of iron stores in the absence of symptomatic anaemia may justify withholding iron supplementation in selected cases.[96] Regular screening for retinopathy is mandatory, and clinicians caring for sickle cell patients should be aware of specific therapies available for complications such as priapism and leg ulcers, as well as the optimal management of patients undergoing surgery and pregnant patients.[36,73,74,97,98]
Even though many experimental pharmacological therapies have been, and are being studied, only hydroxyurea (HU) has been proven to reduce the incidence of painful crises and ACSs, as well as the transfusion requirement, in highly symptomatic patients.[99,100] HU, a ribonucleotide reductase inhibitor employed in myeloproliferative diseases, has been shown to elevate the HbF% in patients with SCD. The long-term efficacy with regard to both morbidity and mortality in adults has recently been reported, and HU may be relatively safe and effective in preventing complications in paediatric patients as well, although major complications still occur despite HU therapy in both children and adults. Furthermore, it is estimated that 40% of patients do not respond to HU treatment at all.[100-104] HU treatment is not without risk of significant side effects such as myelosuppression and leg ulceration, and the potential risk of malignancies with long-term HU exposure is also a source of concern.[88,101,105-109] Therefore, HU therapy is currently limited to clinically severely affected patients and requires intensive patient monitoring.

For severely affected patients, judicious use of red cell transfusions may be the most powerful therapeutic for preventing major SCD-related complications, and general transfusion guidelines for SCD have recently been published.[110,111]
Chronic red cell transfusion programmes aimed at reducing the HbS% below 30% in patients with stroke significantly reduce the risk of stroke recurrence.[88] In children at high risk for first stroke (assessed by detecting abnormal blood flow velocity in large intracranial arteries with transcranial Doppler ultrasonography), chronic transfusions greatly reduce the incidence of a first cerebrovascular event, as well as painful crises and ACS.[110,112] However, such therapies are intensive, the optimal duration is not known, and transfusion-related complications, such as alloimmunisation, infections and iron overload, are of major concern.[101,113]
For major surgery (including cholecystectomy), simple preoperative transfusion is indicated as it reduces the incidence of serious SCD-related postoperative complications.[25,97,114] Clearly, transfusions are not indicated for treatment of uncomplicated painful crises or for correction of steady state anaemia in absence of anaemia-related symptoms or complications (such as heart failure).[111] 'On top' transfusions (administering additional red cell units without removing sickle blood) can precipitate vaso-occlusive complications due to increments in whole blood viscosity, and should be reserved for symptomatic anaemia or severe hypoxemia.[115-117] Exchange transfusions (or erythrocytapheresis if available) are preferred when the patient has a relatively high haemoglobin level and/or is expected to receive multiple transfusions.[115] This results in little net iron gain and keeps whole blood viscosity unchanged. In case of iron overload, stringent adherence to iron chelation therapy is imperative for transfusion therapy to be continued. Expanding the blood donor population of African descent will reduce exposure of sickle cell patients to red cell antigens for which they are mostly negative. Ideally, after extended red cell phenotyping, patients should receive phenotypically matched blood in order to reduce the incidence of alloimunisation.[118]
In highly selected patients, therapy with bone marrow transplantation (BMT) has resulted in impressive disease amelioration, but carries the risk of major morbidity with a significant risk of mortality.[88,100,101,119,120] Importantly, severely affected young patients (e.g. multiple painful events and/or strokes) with relatively normal heart, lung, and kidney function (without severe residual neurological damage due to stroke) may be eligible for BMT and should be referred to specialised centres in a timely fashion. The implementation of BMT is, however, limited due to donor availability, the poor ability to predict a severe clinical course before significant organ damage has occurred (see below), the morbidity associated with the procedure and the availability of transplant centres. New developments in BMT (such as nonmyeloablative regimens, so called 'mini-transplants') may lead to wider applicability. Gene therapy is being explored in animal models, but is not likely to benefit patients in the near future.[100]

OUTCOME AND DETERMINANTS OF DISEASE COURSE

Life expectancy is on the rise for sickle cell patients, but is still shorter than that of the general population. Male and female patients with HbSS are reported to have a median life expectancy of 42 and 48 years respectively, whereas male and female HbSC patients may survive into the seventh decade.[37,51] However, in some parts of Africa, SCD is still often lethal in childhood.[20] Apart from its somatic manifestations, SCD impacts individuals and their families both socially and physiologically when trying to meet

the demands of this chronic illness. Due to its unpredictable and debilitating nature, SCD often interferes with educational development as well.

It is generally accepted that patients with an HbSS and HbSβ°-thalassaemia genotype have severe forms of SCD, while patients with HbSβ⁺-thalassaemia and HbSC run relatively milder disease courses. However, both HbSC and HbSβ⁺-thalassaemia patients are not exempt from major SCD-related complications.[30,31,37,39] Alpha-thalassaemia may confer protection for some major clinical events in HbSS patients, but is associated with more pain, whereas in HbSC patients α-thalassaemia may be of overall benefit.[20,31] The SCD modifying effect of α-thalassaemia is more outspoken with a greater number of α gene deletions. Beta-globin gene haplotypes also influence the clinical course of SCD, especially in patients with the Arab/Indian haplotype, which is associated with a higher HbF% and a generally milder clinical course.[20] However, complications occur in all haplotypes, and the interpretation of haplotype effects are obscured by acquired racial diversity of patients. The HbF% rapidly declines in the first months of life, and stabilises early in the first decade.[6] The protective role of a high HbF% is well established, with mortality being higher in patients with a relatively low HbF%.[37,51,121] Especially in patients with 'hereditary persistence of faetal haemoglobin', in whom HbF% exceeds 20%, there are usually no disease manifestations.[20] HbF% tends to be higher in females, which could be a possible explanation for their longer life expectancy.[20,30,37] The protective effect of a high HbF% is relative, as patients with a severe clinical course and a high HbF% have been described, as well as elderly HbSS patients with a low HbF%.[20,38,122,123] Relatively high levels of haemoglobin with a low HbF% are associated with higher pain rates, necrosis of the femoral head, retinopathy and ACS, whereas low haemoglobin levels are a risk factor for brain injury and early death in both children and adults.[20,30,37,46,51,52,58] Children who experience a hand-foot syndrome in the first year of life also tend to experience more major SCD-related complications.[27,58] Leucocytosis in the absence of infection is associated with the occurrence of major clinical events in children such as stroke, and is a risk factor for early death in adults and children.[37,51,52,58] Environmental factors, as well as socioeconomic status, may also influence the clinical course of SCD.[20,121]

CONCLUSION

SCD, in its various forms, is a serious debilitating disease affecting many people worldwide. Chronic haemolytic anaemia and vaso-occlusion in almost all organs leads to significant morbidity and early death. A key issue in managing sickle cell patients is the early identification of high-risk subjects for poor outcome, in order to initiate treatment prior to the development of debilitating organ damage. This is of cardinal importance given the potential side effects of therapeutics such as hydroxyurea, chronic red cell transfusions and bone marrow transplantation. However, it may be concluded from the above that there are currently few reliable objective laboratory tools that can aid the clinician with risk stratification in the daily management of individuals with SCD. Available data regarding the effect of haemoglobin levels and leucocyte counts, as well as epistatic effects of HbF%, β-globin haplotypes and concurrent α-thalassaemia are derived mostly from large epidemiological studies and are difficult to apply to an individual patient. Considerable lack of knowledge still exists regarding determinants of SCD severity, and monitoring sickle cell patients solely by relying on clinical manifestations may also not be accurate. Identification of new risk factors for poor outcome and objective markers for monitoring patients with SCD are needed, as are safer and more widely applicable therapeutics.[40] In this light, it is encouraging that SCD is now included in structural governmental programmes for disease prevention and management in the Netherlands.[124]

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