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Sickle Cell Disease in Children

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Abstract

Early identification of infants with sickle cell disease (SCD) by newborn screening, now universal in all 50 states in the US, has improved survival, mainly by preventing overwhelming sepsis with the early use of prophylactic penicillin. Routine transcranial Doppler screening with the institution of chronic transfusion decreases the risk of stroke from 10% to 1% in paediatric SCD patients. Hydroxyurea decreases the number and frequency of painful crises, acute chest syndromes and number of blood transfusions in children with SCD. Genetic research continues to be driven toward the prevention and ultimate cure of SCD before adulthood. This review focuses on clinical manifestations and therapeutic strategies for paediatric SCD as well as the evolving topic of gene-focused prevention and therapy.

1. Introduction and Background

Sickle cell anaemia (SCA; homozygous sickle haemoglobin [HbS], i.e. HbSS) occurs when thymine is substituted for adenine in the 6th codon of the beta globin gene, resulting in the production of valine (a hydrophobic amino acid) instead of glutamic acid, which is hydrophilic. Although all SCA patients share the same genetic mutation, the clinical course is highly variable between patients.[1] The highest sickle cell trait (HbAS) carrier rate is present in families who trace their ancestry to malaria endemic regions. In addition to homozygous SCA, other sickle-related haemoglobinopathies occur when HbS is inherited in the heterozygous state with another beta globin chain mutation (most commonly HbC, i.e. HbSC) or quantitative defects in beta globin production ($HbS\beta^0$thalassaemia and $HbS\beta^+$thalassaemia). Both $HbS\beta^0$thalassaemia and HbSS are clinically severe, while patients with HbSC and $HbS\beta^+$thalassaemia generally have milder phenotypes. One in 500 African American infants born in the US is affected by sickle cell disease (SCD) [which includes SCA and the compound heterozygous sickle haemoglobinopathies], and it is estimated that nearly 100 000 SCD patients live in the US.[2]

A hallmark of SCD is chronic haemolysis with concomitant vaso-occlusion caused by polymerization of HbS molecules. Polymerization usually occurs during hypoxia, acidosis or in the setting of pyrexia or dehydration. The haemoglobin molecules polymerize and form linear elongated fibres that distort the shape of the red blood cells (RBCs). Sickle RBCs survive an average of 12 to 16 days, approximately one-tenth of the average lifespan of a normal erythrocyte.[3,4] Fetal haemoglobin (HbF, $alpha_2$,$gamma_2$) prevents polymerization of HbS, but needs to be at a high enough concentration within each RBC to prevent haemolysis. HbF fractions of 20% have been demonstrated to reduce haemolysis in clinical studies as well as in experimental models.[5-8] Hence, sickle RBCs that contain large amounts of HbF (F-cells) survive 5–7 times longer than cells with low HbF concentrations.[3] Increased HbF levels are correlated with decreased mortality and painful crises in adults with SCD.[9] However, studies have not fully demonstrated that HbF lowers rates of stroke or pulmonary hypertension.[10,11]

Despite sharing the same genetic mutation, the clinical phenotype of HbSS is highly variable and currently difficult to predict at an early age. The CSSCD (Cooperative Study of Sickle Cell Disease) was a multi-centre study that aimed to elucidate the natural history of SCD, with a goal of identifying early predictors of disease severity.[12] More than 3000 patients, ranging from newborns to adults, were enrolled. In an analysis of 380 newborns enrolled in the CSSCD before age 6 months, severe disease was predicted by dactylitis before age 1 year, baseline haemoglobin <7 g/dL in the second year of life and baseline leukocytosis in the second year of life. Most deaths in this newborn cohort were due to infection or stroke.[13] Investigators in Dallas (US) recently re-examined these three predictor variables using a cohort largely assembled during the era of penicillin prophylaxis and transcranial Doppler (TCD) screening. None of the three previously identified variables were associated with a severe disease course. Improved supportive care, with decreases in infectious deaths and stroke rate, could account for the differences in outcomes between the two studies.[14] Currently, paediatric haematologists remain unable to predict which infants will be most severely affected by SCD during childhood. The aim of this review is to provide readers with a succinct update on the clinical manifestations of SCD during the first 2 decades of life as well as strategies for prevention of SCD complications. In addition to existing therapies, the review will focus upon translational research targeting the globin genes.

2. Manifestation and Sequelae of Sickle Cell Disease (SCD) in Infants and Children

Splenic sequestration occurs in as many as 30% of SCD patients at less than 6 years of age.[15] Acute splenic sequestration (ASS) may be classified as major or minor episodes. Major episodes are life threatening, with rapid enlargement of the spleen and circulatory collapse requiring

transfusion. Minor episodes also involve rapid enlargement of the spleen, but the haemoglobin reduction is less severe (absolute values remaining above 6 g/dL).[16,17] A decreased mortality rate from ASS may be achieved with repeated education about splenic palpation techniques for parents of SCD infants during comprehensive clinic visits. While mortality decreased, the incidence of ASS increased, likely due to heightened awareness and detection of the disorder.[15] Ultimately, the splenic pathology places SCD patients at higher risk for infection with encapsulated organisms than healthy children of similar age.[18,19] Functional asplenia is present in over 80% of HbSS and HbSβ^0thalassaemia patients before 1 year of age.[20] Auto-infarction of the spleen is usually complete by age 5 years in HbSS and HbSβ^0thalassaemia patients, while HbSC and HbSβ^+thalassaemia patients remain at risk for splenic sequestration throughout their lives. The oldest reported age of an HbSC patient with splenic sequestration is 44 years.[21]

Pain is the hallmark of SCD. Infants are generally spared from this complication because of their elevated HbF levels. The first episode of pain often occurs in the small bones of the hands and feet and is termed 'dactylitis'. Approximately half of children with SCD develop dactylitis by age 2 years.[22] Previously thought to be a predictor of disease severity, children who experienced dactylitis did not have more severe SCD when a contemporary cohort was analysed.[14] The frequency and severity of pain is variable among patients; over one-third of the nearly 3600 SCD patients enrolled in the CSSCD had no episodes of severe pain, while 1% had more than six episodes of severe pain per year.[23] Between 50% and 60% of all emergency room visits by paediatric SCD patients are for painful events,[24,25] and between 60% and 80% of hospitalizations for paediatric SCD patients are pain related.[26,27]

Acute chest syndrome (ACS) is a life-threatening complication of SCD with peak incidence in early childhood.[28] Nearly 30% of SCD patients had at least one episode of ACS, with incidence of ACS being the highest in HbSS and HbSβ^0thalassaemia patients when compared with HbSC and HbSβ^+thalassaemia[29] (see table I). ACS is defined as an infiltrate on the chest x-ray in an SCD patient accompanied by two or more of the following: fever, cough, wheezing, tachypnea or chest pain. The aetiology of ACS is multi-factorial and difficult to determine at the time of diagnosis. Aetiologies for ACS include pulmonary fat embolism, infection, sickling phenomenon, fluid overload and atelectasis that occurs due to hypoventilation from oversedation or inadequate pain control that can lead to splinting.

Table I. Clinical sequelae of sickle cell disease

Clinical sequelae	Genotypes affected	Treatment	Prevention
Infection, *Streptococcus pneumoniae* sepsis	HbSS = HSβ^0thal >HbSC>HbSβ^+thal	IV antibiotics	Penicillin prophylaxis
Pain crisis	HbSS = HSβ^0thal >HbSC>HbSβ^+thal	Non-steroidal anti-inflammatories, narcotics (PO or IV), IV fluids	Hydroxyurea, chronic transfusions, HSCT
Acute chest syndrome	HbSS = HSβ^0thal >HbSC>HbSβ^+thal	Antibacterials (cephalosporins, macrolides), pain medications (NSAIDs, narcotics), IV fluids	Incentive spirometry, hydroxyurea, chronic transfusions, HSCT, asthma management
Overt stroke	HbSS = HSβ^0thal >HbSC>HbSβ^+thal	Chronic transfusions, HSCT	Annual TCD screening
Silent cerebral infarction	HbSS = HSβ^0thal >HbSC>HbSβ^+thal	Unknown	Unknown
SCD retinopathy	HbSC>HbSS = HSβ^0thal >HbSβ^+thal	Laser	Annual ophthalmologic exams
Avascular necrosis	HbSC>HbSS = HSβ^0thal >HbSβ^+thal	Physical therapy, surgical intervention	Comprehensive joint exam
SCD nephropathy	HbSS = HSβ^0thal>HbSC>HbSβ^+thal	ACE inhibitors	HU, chronic transfusions

ACE = angiotensin-converting enzyme; **HbSS** = sickle cell anaemia; **HSCT** = haematopoietic stem cell transplant; **HU** = hydroxyurea; **IV** = intravenous; **PO** = by mouth; **SCD** = sickle cell disease; **TCD** = transcranial Doppler; **thal** = thalassaemia.

Prior to the onset of TCD screening, stroke occurred in 10% of SCD patients before age 20 years. The STOP (Stroke Prevention in Sickle Cell Anaemia) study demonstrated that annual, routine screening with TCD could decrease the stroke rate from 10% to 1% in children with HbSS and HbSβ^0thalassaemia.[30] TCD detects large vessel disease in patients with SCD. The large vessels are most likely involved in overt stroke in SCD. Time-averaged mean of the maximum (TAMM) velocities are either normal (<170 cm/second), conditional (170–199 cm/second) or abnormal (≥200 cm/second). Normal TCDs should be repeated annually. Conditional TCDs should be repeated at 3–6 month intervals, while abnormal TCDs designate the children at highest risk for stroke. In most centres, abnormal TCDs are repeated within 2–4 weeks of the initial study.[31,32] If the TCD velocity is confirmed to be abnormal, chronic blood transfusions should be initiated. The goal of chronic monthly blood transfusion therapy is to maintain HbS at less than 30%.

Silent cerebral infarct (SCI) has increasingly been recognized as a significant complication of SCD. CSSCD data demonstrated that 17% of children with SCD were affected, but more recent studies place the prevalence at 35–40%.[33-35] SCI has important implications for school achievement and developmental delay. The ongoing Silent Infarct Transfusion Trial[36] is the first randomized controlled trial investigating the best treatment for SCI.[37] No predictive test for SCI currently exists, though data from the BABY HUG (Pediatric Hydroxyurea in Sickle Cell Anemia) trial suggests that SCI occurs early in life. Early in the BABY HUG trial, 23 infants had a brain MRI/magnetic resonance angiogram (MRA) as part of the study eligibility evaluation. Mean age of screening was 13.7 months, and 13% (3/23) of the subjects were found to have SCI. Brain MRA was normal in all of the screened study participants.[38] Brain MRI/MRA was discontinued as part of the screening evaluation after a sedation-related death prior to the MRI.

While urinary concentrating defects (hyposthenuria) and glomerular hyperfiltration are common in young SCD patients,[39] SCD nephropathy is relatively rare in paediatric SCD patients, with incidence increasing during adolescence. One of the earliest signs of SCD nephropathy is asymptomatic proteinuria, ranging from microalbuminuria to macroalbuminuria. Albuminuria is the most sensitive marker for SCD nephropathy. Serum creatinine is not a sensitive marker for SCD nephropathy because of increased glomerular filtration rate (GFR) and increased tubular secretion of creatinine in SCD patients.[39,40] Over 30% of adult SCD patients will develop chronic renal failure, with 10% of those patients progressing to end-stage renal disease (ESRD).[40] ESRD is a leading cause of death in adults with SCD.

Proliferative sickle retinopathy (PSR) also affects children with SCD. It is rare in the first decade of life, and incidence increases in the second decade, with the peak prevalence of PSR occurring between ages 15 and 24 years in male HbSC patients. PSR in other SCD patients is usually delayed until adulthood.[41] The rate of PSR in HbSC patients is three times higher than in HbSS/HbSβ^0thalassaemia patients, most likely due to increased viscosity.[42]

Additional manifestations of SCD are less commonly diagnosed in the paediatric population. Avascular necrosis (AVN) occurs in almost half of SCD patients by the 4th decade of life and occurs earlier in life in HbSC patients than in HbSS patients, again most likely due to hyperviscosity seen in HbSC patients. The femoral head is the bone most commonly affected by AVN, with the humeral head the second most commonly affected. When AVN is suspected, MRI should be used to image the affected joint.[43] Pulmonary hypertension is associated with increased mortality in adult SCD patients, but this association has not been shown in paediatric SCD patients.[11,44]

3. Prevention and Treatment Strategies

3.1 Splenectomy

Almost 50% of patients who experience one episode of ASS are at risk for recurrent splenic sequestration that may require splenectomy.[15] Splenectomy should be deferred until 2–3 years of age to allow for proper vaccination against

encapsulated organisms. Guidelines have been proposed for splenectomy based on the frequency and severity of the ASS episodes.[17] If recurrent ASS occurs before 2 years of age, patients can be maintained with chronic monthly blood transfusions to keep HbS at less than 30% until a safer age for splenectomy is reached.[45]

3.2 Vaccination and Penicillin Prophylaxis

Newborn screening has revolutionized the care of SCD patients by allowing early identification of affected infants. The PROPS (Prophylactic Penicillin Study) was a randomized, double-blind, placebo-controlled study of penicillin that was stopped early because of an 85% decrease in the rate of pneumococcal infection in the children receiving penicillin.[46] Penicillin prophylaxis should be instituted before 2 months of age at an oral dose of 125 mg twice daily. The dose should be increased to 250 mg twice daily at age 3 years to account for physical growth of the child. Routine prophylactic penicillin coupled with immunization against *Streptococcus pneumoniae*, with both the 23-valent pneumococcal vaccine (Pneumovax®) and the protein-conjugated pneumococcal vaccine (PCV, Prevnar®) series, has drastically reduced the rate of invasive pneumococcal disease (IPD), but IPD continues to be a problem in SCD patients.[19] The PROPS follow-up study (PROPS 2) examined the duration of penicillin prophylaxis. PROPS 2 demonstrated that there was no increased rate of *S. pneumoniae* bacteraemia in children who stopped their penicillin prophylaxis at age 5 years, provided that they had received two doses of Pneumovax®, had no history of *S. pneumoniae* bacteraemia and had not undergone surgical splenectomy.[47] Splenectomized patients should be maintained on twice-daily penicillin prophylaxis throughout life to minimize the risk of overwhelming bacterial infection and sepsis-related death.[48] (Please see table I for more information about prevention of common SCD sequelae.)

The vaso-occlusion of SCD places paediatric patients at increased risk of infectious complications. Thus, vaccination in paediatric SCD patients represents an important aspect of their preventive care.[49] At age 2 and 5 years, paediatric patients should receive Pneumovax®. SCD patients should also receive the quadrivalent meningococcal vaccine at age 2 years as the Advisory Committee on Immunization Practices (ACIP) recently recommended vaccination starting at age 2 years for populations at increased risk of invasive meningococcal disease.[50] Annual influenza vaccination is recommended because paediatric SCD patients are more likely to require hospitalization for influenza-related complications and experience more complications from influenza infections than children without SCD.[51]

3.3 Acute Chest Syndrome (ACS)

3.3.1 Prevention of ACS

SCD patients who are admitted with acute vaso-occlusive crisis (VOC) are at risk of developing ACS, particularly if chest or back pain limits the depth of inspiration and leads to splinting.[52] Oversedation from pain medication can also contribute to the development of ACS, so standardized doses of pain medication and use of patient-controlled analgesia (PCA) are important in the prevention of ACS. Equally important is the regular use of incentive spirometry (IS) to prevent dependent atelectasis, which has been shown to be an effective therapy in the prevention of ACS.[52] SCD patients are at increased risk for ACS in the post-operative period. Pre-operative intravenous fluids while the patient is nil by mouth and blood transfusions (haemoglobin target of 10 g/dL) have been shown to decrease, though not completely eliminate, the risk of ACS in the post-operative period.[53]

3.3.2 Treatment of ACS

Treatment strategies for ACS should be multifaceted to address its multiple potential causes and include broad-spectrum antibacterials (a cephalosporin and a macrolide for atypical pneumonia coverage), intravenous fluids (usually given at a lower rate than that used for pain to minimize the risk for pulmonary oedema, which will exacerbate pulmonary symptoms), pain medications (type and administration based on the patient's report), incentive spirometry and other pulmonary methodologies.[29,54,55] Blood transfusion should be reserved for patients with increased oxygen

requirements. Exchange transfusions may be helpful for patients whose clinical condition is rapidly deteriorating or who are requiring positive pressure ventilator support with either bilevel positive airway pressure (BiPAP) or mechanical ventilation.[55] Recommendations and efficacy for the use of systemic steroids in this setting are inconsistent.[56-59] One prospective study found that hospital length of stay was reduced by 40% in patients who received systemic steroids, but the rate of re-admission for pain was increased.[60] Importantly, the use of systemic steroids has been associated with an increased rate of haemorrhagic stroke, though the exact cause of the stroke is difficult to determine in retrospective analyses and is likely multi-factorial.[61] SCD patients who also have asthma are at increased risk for ACS and have more frequent episodes of ACS. Measures to control asthma (inhaled corticosteroids and beta agonists for acute exacerbations) may help in preventing subsequent ACS. Initial reports also suggest that inhaled nitric oxide (NO) in cases of severe ACS may improve oxygenation and decrease required respiratory support.[62-64]

3.4 Pain Management

When patients receive treatment for pain in a hospital or clinic setting, an integrated approach is employed that includes intravenous fluids (to treat dehydration), intravenous analgesics (narcotics and non-steroidal anti-inflammatories) and non-pharmacological pain management techniques, including heat packs, relaxation, breathing exercises and therapeutic exercises. Despite frequent use of narcotics for painful episodes, the incidence of narcotic dependence in SCD patients is not reportedly different from that in the general population (range 3–10% of patients).[65]

3.5 Chronic Transfusions and Iron Management

Blood transfusions are indicated in a limited number of clinical situations in SCD patients. RBC exchange is warranted in the face of an acute, overt stroke or life-threatening ACS with impending respiratory failure. Stroke patients are continued on monthly RBC transfusions indefinitely, with a goal HbS of less than 30%. Patients who have had a life-threatening episode of ACS may be maintained on chronic monthly RBC transfusions for a 6-month period to allow time for lung healing.[45,66] Patients with recurrent splenic sequestration may also be maintained on chronic monthly RBC transfusions until they reach an age that is safe for splenectomy (age 2–3 years).[45] Patients who have had abnormal TCDs are also treated with monthly transfusions, with a goal HbS of 30%. Complications of chronic transfusions include alloimmunization, iron overload and infection. The rate of alloimmunization in SCD patients is between 20% and 40%.[67]

One unit of transfused RBCs contains 250 mg of iron, but healthy adults excrete only 1–2 mg each day.[68] Therefore, SCD patients who receive monthly RBC transfusions predictably develop severe iron overload after 10–20 transfusions (100–200 mL RBCs/kg). As such, transfusional haemochromatosis is a significant problem in chronically transfused SCD patients.[69,70] Cardiac haemosiderosis is relatively uncommon in SCD, as excess iron is stored in the liver and reticuloendothelial system.[71]

Prior to 2005, the only available iron chelator was deferoxamine which, because of its poor oral availability and short half-life, requires subcutaneous infusions that last 8–10 hours 5 nights each week. Not unexpectedly, the compliance rate for this medication and delivery system was low. In 2005, deferasirox received US FDA approval and provided an orally available option. First approved for treatment of iron overload in β-thalassaemia patients, deferasirox 20 mg/kg/day showed non-inferiority in maintaining serum ferritin and reducing liver iron content (LIC) compared with deferoxamine when used in patients with SCD. Deferasirox doses of 30 mg/kg/day reduced both serum ferritin and LIC.[72] In select cases where ferritin and LIC levels are not adequately controlled, deferasirox doses can be increased up to 40 mg/kg/day.[73] Retrospective analysis of four clinical trials demonstrated that serum ferritin was significantly decreased, with no significant increase in medication-related adverse effects.[73] Both deferoxamine and deferasirox require regular screening for ophthalmological

changes, ototoxicity and renal and hepatic toxicity. Serum ferritin should be monitored at monthly intervals and deferasirox dosing should be adjusted accordingly.[74]

3.6 Hydroxyurea

Hydroxyurea is the only FDA-approved medication to treat adults with SCD. In paediatric SCD patients, the starting hydroxyurea dose is 15–20 mg/kg/day and is escalated by 5 mg/kg/day increments until the goal dose of 30–35 mg/kg/day is reached.[75,76] If patients experience myelosuppression (absolute neutrophil count <1500/microlitre, platelet count <80 000/microlitre and absolute reticulocyte count of <100 000/microlitre), hydroxyurea should be held for 2 weeks and the complete blood count (CBC) should be repeated. If the myelosuppression resolves after 2 weeks, the medication should be restarted at the previous dose. If the myelosuppression persists, the medication should be held for 2 more weeks, with CBC repeated. Hydroxyurea may be restarted at the previous dose if the blood counts have normalized, but should be restarted at a decreased dose if the myelosuppression persists.

A double-blind randomized controlled trial of hydroxyurea in adults revealed lower rates of painful crises, ACS and unscheduled blood transfusions in patients treated with hydroxyurea.[77] These results were recently confirmed in a multicentre, double-blind, randomized controlled trial of hydroxyurea in young children with SCD (BABY HUG).[78] The primary endpoints of the BABY HUG study (renal and splenic function in young children) were not satisfied. Infants enrolled on the BABY HUG study were maintained at a dose of hydroxyurea 20 mg/kg/day with no dose escalation. Study participants were enrolled irrespective of disease severity. No growth or developmental delay was noted in the infants who were assigned to the hydroxyurea arm when compared with the placebo group. Rates or severity of infections were not increased in the hydroxyurea group. Based on these data, hydroxyurea can be safely administered in young children with SCD at 20 mg/kg/day, although the use of hydroxyurea without any preceding SCD-related sequelae may be highly variable among practitioners and centres.

3.7 Treatment for Other SCD Sequelae

Mixed reports exist on the benefits of hydroxyurea in preventing or reversing SCD nephropathy in all ages. Proteinuria can be reduced with angiotensin-converting enzyme (ACE) inhibitors in diabetic and non-diabetic nephropathy.[40,79] Treatment guidelines for ACE inhibitor use in SCD patients are needed to guide timing of treatment or dosing, and involvement of a nephrologist with experience in treating SCD nephropathy is recommended. Annual ophthalmological screening should start early in the second decade of life in SCD patients, as early detection and intervention can prevent vision loss. Surgical intervention is based on the location of lesions and the degree of macular involvement.[41] Interventions for AVN include physical therapy and surgical intervention. Initial surgical intervention techniques are usually aimed at improving blood flow to the affected bone (bone coring procedures), with joint replacement reserved for the most severe cases.

4. Potential Globin Gene-Targeted Therapies

Infants with SCD develop clinical symptoms of the disease during early childhood largely due to lost expression of HbF. In rare cases, SCD patients inherit the ability to express high levels of HbF throughout their lives. In those cases, the SCD disease course is mild.[80] Aside from HbF expression, it must also be remembered that SCD is an autosomal recessive disorder, so correction of a single allele should be curative. As such, strategies aimed toward modulation, addition, replacement or correction of the globin genes continue to evolve in the basic and clinical research settings. Effective therapy should prevent severe SCD sequelae if instituted early in life.

4.1 Gamma Globin Gene Modulation

Hydroxyurea inhibits ribonucleotide reductase, which has a cytotoxic effect in haematopoietic stem cells and causes increased HbF levels.[81]

Azacytadine also induces HbF production in animal models and showed similar results in small studies of SCD and β-thalassaemia patients.[82,83] Larger clinical trials have not been pursued because of difficulties with the drug administration and the perception of malignancy risk with this drug. Short courses of butyrate, involved in histone deacetylation, also increase HbF levels in haemoglobinopathy patients. However, its use has been limited by lack of a sustained HbF response and by patient compliance issues.[84] A recent study found that butyrate may be an effective adjunct therapy for leg ulcers in adults with SCD.[85] In humans, the erythroid regenerative stress that occurs after bone marrow transplantation is associated with a more robust increase in erythropoietin levels and increased expression of HbF.[86,87] While early hypotheses proposed that increased HbF levels occurred as a result of altered cell maturation kinetics,[88] related modification signal transduction in immature erythroblasts was additionally proposed as a potential 'stress' mechanism.[89]

For decades, efforts have been made to understand globin gene switching in order to better approach therapeutic manipulation of the fetal (gamma) globin genes. A main focus of research involves the study of globin locus chromatin, as well as the transcription factors that may regulate globin gene switching and transcription. With the mapping of the human genome, genome-wide association studies (GWAS) were also pursued in subjects with high and low levels of HbF to identify genes that were important in HbF expression. Recently, BCL11A, a transcription factor located on chromosome 2p15, was identified as playing an important role in the regulation of HbF expression. In the initial study, BCL11A was found to account for 15% of the variability in HbF levels between the two populations.[90] Murine BCL11A knock down models consistently have higher levels of HbF than the wild type animals, and a recent study in BCL11A knock out mice demonstrated improved SCD phenotype and haematological findings.[91] Targeting BCL11A could potentially increase HbF levels in haemoglobinopathy patients, which could lead to resolution of disease signs and symptoms. BCL11A plays an integral role in B-cell function, necessitating careful evaluation of potentially deleterious effects of knocking down BCL11A in non-erythroid cells.

4.2 Gene Replacement through Haematopoietic Stem Cell Transplant

Currently, the only available cure for SCD is haematopoietic stem cell transplant (HSCT). Conceptually, transplantation represents a cellular method that replaces the sickle gene with cells containing the normal gene. Early trials of HSCT in SCD patients revealed that SCD patients have higher complication rates than other patients undergoing HSCT for non-malignant haematological disorders.[92,93] In paediatric patients, 3-year survival following HSCT is 90%, while it is 62% in adult SCD patients.[93] Ongoing haemolysis and vaso-occlusion with resultant vasculopathy and organ damage are the most likely causes of these discrepant mortality rates.

Matched sibling donor transplants in SCD have excellent overall survival (93–97%) and good event-free survival (85%);[94] however, fewer than 20% of SCD patients have a suitable sibling donor. Therefore, unrelated donor (URD) HSCT is a subject of intense interest. HSCT complications like graft versus host disease (GVHD) are of increased concern given the fact that GVHD has no benefit in non-malignant transplants. Reduced-intensity HSCTs are aimed at reducing conditioning regimen-related toxicities like gonadal dysfunction and secondary malignancies. Reduced-intensity, matched sibling donor transplants were performed in ten adults with severe SCD, and 90% (9/10) maintained stable mixed chimerism that permitted improvement in haemoglobin. Remarkably, none of the transplanted patients experienced acute or chronic GVHD.[95] Successful transplants in children with SCD additionally result in organ damage reversal or stabilization of CNS vasculopathy. SCD patients undergoing HSCT require aggressive supportive care during the preparative regimen and within the first 30–60 days following transplant. In addition to haematological support, special attention is given to the prevention of neurological complications, hypertension and hypomagnesaemia.[92,96]

4.3 Gene Addition or Correction for SCD

SCD, like other monogenetic disorders, is an excellent candidate for experimental gene therapy. Gene addition involving retroviral gene transduction have been developed over the last 2 decades.[97] Currently, gene correction strategies are being developed in order to reduce or eliminate the potentially deleterious effects of viral integration upon the genome.[98] These efforts have been enhanced by the discovery that cellular fates can be reliably reprogrammed.[99] Today, fibroblasts from skin can be manipulated and reprogrammed to become human induced pluripotent stem cells (iPSCs). Zinc finger nucleases are engineered restriction enzymes that create double strand breaks at specific genetic locations.[100,101] At least two independent groups recently demonstrated that the homozygous SCD mutation can be corrected using an approach that combines cell fate reprogramming with zinc finger nucleases.[101,102] Ideally, the zinc finger nucleases will be designed with robust specificity for the HbS allele.

5. Summary and Conclusion

The first clinical description of SCD was made over a century ago. Within that century, advances have been made in the supportive care of SCD patients, which has resulted in longer life expectancy and better quality of life, but important questions remain for further research (table II). Disease-modifying therapy with antibacterial prophylaxis, hydroxyurea and chronic monthly blood transfusions are the current mainstays of therapy. Genetic-based studies are ongoing and will ideally result in curative therapy that will prevent disease-related sequelae.

Table II. Ongoing and future sickle cell disease research questions

Can SCD severity be accurately predicted during early infancy prior to the onset of clinical complications?
Can HbF silencing during the first 6 months of infancy be prevented or modulated to sustain higher HbF levels into adulthood?
Does the combination of HU with other SCD therapies like chronic transfusions improve the clinical outcome?
How can the donor pools for haematopoietic stem cell transplants or blood transfusion therapy be increased for SCD patients?

HbF = fetal haemoglobin; **HU** = hydroxyurea; **SCD** = sickle cell disease.

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