bjh review

Sickle cell nephropathy – a practical approach

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Summary

Despite its apparently simple molecular aetiology, sickle cell disease (SCD) has long been known to have a remarkably variable clinical course, with complications involving many organs including the kidneys. Whilst many affected individuals show no evidence of renal involvement into late adulthood, others develop renal dysfunction in childhood or early adult life with a significant proportion eventually requiring renal replacement therapy. This review explores the pathophysiology and clinical manifestations of sickle cell nephropathy (SCN) and discusses how each complication can be investigated, monitored and managed in the outpatient setting. We summarize current knowledge of genetic modulation of sickle-related renal dysfunction. We outline the evidence for various treatment options and discuss others for which little evidence currently exists.

Keywords: sickle cell disease, chronic kidney disease, proteinuria, dialysis, transplantation.

Sickle cell disease (SCD) is endemic in malaria-prevalent regions due to the protective nature of the carrier state (Piel *et al*, 2010). Recent population movements however, mean that it is becoming increasingly common in non-endemic regions (Modell *et al*, 2007). There are currently over 300 000 people in England and Wales who carry the gene for haemoglobin S or haemoglobin C and over 12 000 individuals affected with SCD living in the UK. Although antenatal screening and prenatal diagnosis are widely available, approximately 360 affected live births still occur per annum in this country (http://www.screening.nhs.uk/sickleandthal). These changes now present healthcare professionals with the challenge of providing adequate services for treatment of sickle cell disorders and their complications. Renal complications are a well-known cause of morbidity and mortality in SCD, and the incidence of renal failure increases as patient survival improves.

Undoubtedly environmental factors play a role as well as co-inherited genetic factors for the development of chronic kidney disease (CKD). The onset of CKD is insidious and the multifactorial aetiology requires on-going vigilance and monitoring of patients to detect those that are most at risk of developing significant renal complications. Microalbuminuria, though an early manifestation of sickle cell nephropathy (SCN), reaches a prevalence of approximately 60% in those over 45 years but only 4–12% of patients will develop the serious and life-threatening complication of end-stage renal disease (ESRD) (Powars *et al*, 2005; Guasch *et al*, 2006).

It is important to note that not all renal disease in patients with SCD is due to SCN. Patients with SCD may develop renal dysfunction/proteinuria from other causes, such as lupus nephritis and Hepatitis C virus or human immunodeficiency virus (HIV)-associated nephropathy. The presence of these conditions should be considered in the investigation of any patient with renal disease and histological evidence sought if suspected (Table I). There is also no pathognomonic lesion that defines SCN. Glomerular hypertrophy with distended capillaries is universally found but is not confined to those who have developed microalbuminuria or proteinuria. Focal and segmental glomerular sclerosis (FSGS) is the most common lesion associated with proteinuria, but is not specific to SCN as it is associated with many other proteinuric renal diseases. Other lesions that have been demonstrated on biopsy include thrombotic microangiopathy (TMA) and membranoproliferative glomerulonephritis (MPGN), lesions also not exclusive to SCN (Maigne *et al*, 2010). The only frequently demonstrated interstitial lesion is abundant haemosiderin granules in proximal tubular epithelial cells (Maigne *et al*, 2010). Renal iron deposition has also been noted on magnetic resonance scans in patients with SCD but appears not to be related to liver iron concentration, a marker of total body iron load. Renal iron, however, does appear to be correlated with lactate dyhydrogenase, a marker of haemolysis, but so far has not been shown to be associated with renal dysfunction or degree of albuminuria (Schein *et al*, 2008).

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Table I. Recommended investigations for patients with proteinuria.

Immunology for lupus nephritis
Autoantibodies
Double-stranded DNA antibodies
Complement levels
Virus serology
Human immunodeficiency virus
Hepatitis B
Hepatitis C
Human parvovirus B19 (if new-onset nephrotic syndrome or recent transient red cell aplasia
Myeloma screen (if >40 years old)
Renal tract ultrasound scan
Consider renal biopsy if any of 1–3 is positive or acute onset nephrotic syndrome

Pathophysiology of SCN

To understand the pathophysiology of SCN, a little must be explained about the normal physiology of the kidney. For the kidneys to achieve their goal of effectively filtering the plasma at a rate of approximately 100 ml/min/1·73 m^2, they receive about 25% of the cardiac output despite contributing <1% of total body weight (O'Connor *et al*, 2006). This blood enters the outer segment or cortex of the kidney and the resulting excess oxygen delivery to this region is mitigated by shunting of oxygen from the afferent arteriole entering each glomerulus, to the efferent arteriole. The vessels (vasa recta) that supply the inner segment or medulla of the kidney branch off early from the efferent arteriole taking only a fraction of the total renal blood flow with them. A large proportion of the blood that enters the renal cortex is therefore delivered back to the venous circulation without entering the medulla at all. The maintenance of a relatively poor but intricate medullary blood flow is critical for maintaining the cortico-medullary interstitial solute gradient that drives water and solute reabsorption and which allows for effective urinary concentration (Evans *et al*, 2008).

The resulting relative hypoxia (partial pressure of oxygen 10–35 mmHg), the acidosis and the hyperosmolarity of the inner medulla make it an ideal environment for the polymerisation of deoxygenated haemoglobin S and subsequent sickling of erythrocytes. It has previously been hypothesized that, over time, repeated cycles of sickling lead to ischaemic injury and microinfarcts, which in turn give rise to the chronic microvascular disease and reduced medullary blood flow that are apparent in established SCN. The subsequent worsening of the hypoxia stimulates localized prostaglandin release and marked vasodilation, which increases renal blood flow and hence glomerular filtration rate (GFR). Persistently raised GFR eventually gives rise to proteinuria and glomerulosclerosis, which together with tubulointerstitial fibrosis lead to the picture of progressive CKD (de Jong & Statius van Eps, 1985; Scheinman, 2009). Recent observational studies have suggested that microalbuminuria and hyperfiltration may be associated with the more haemolytic phenotype of the SCD spectrum (de Jong & Statius van Eps, 1985; Guasch *et al*, 2006; Scheinman, 2009; Haymann *et al*, 2010; Maier-Redelsperger *et al*, 2010). It seems that in addition to the intermittent, localized microvascular occlusion, renovascular pathology may be a simultaneous target of multi-organ vasculopathy related to the chronic nitric oxide (NO) depletion from the ongoing intravascular haemolysis (Kato *et al*, 2009). In addition, the activation of hypoxia inducible factor 1α (HIF1α) and the consequent increase in local Endothelin-1 release, in the presence of reduced nitric oxide, leads to an increase in reactive oxygen species and vasoconstriction, thus feeding in to a cycle of chronic medullary hypoxia (Gurbanov *et al*, 1996; Heyman *et al*, 2008). NO deficiency has also been demonstrated to lead to CKD in people without SCD (Baylis, 2008) so, whilst there is mounting evidence that this consequence of chronic haemolysis is pivotal to the pathogenesis of the pulmonary hypertension associated with SCD, it is undoubtedly also a factor in the progression of SCN (Gordeuk *et al*, 2008). In keeping with this, soluble fms-like tyrosine kinase-1 (sFLT-1) has recently been found to be upregulated (over baseline) in patients with both SCD-associated pulmonary hypertension and albuminuria. It is a member of the vascular endothelial growth factor (VEGF) receptor family and acts as a potent VEGF inhibitor by adhering to its receptor-binding domain. It has previously been implicated in the pathogenesis of pre-eclampsia and cardiovascular disease associated with CKD and is coupled with a reduction in NO production resulting in endothelial dysfunction and vasculopathy (Di Marco *et al*, 2009; Ataga *et al*, 2011).

Hyperfiltration

The early signs of SCN include the presence of abnormally large and distended glomeruli that has been reported in children as young as 2 years and it has long been understood that the total renal blood flow (RBF) and hence GFR are increased from a young age (Fig 1) (Bernstein & Whitten, 1960; de Jong & Statius van Eps, 1985; Schmitt *et al*, 1998; Wesson, 2002). Indeed, the recently reported BABY HUG trial, designed to assess the impact of hydroxycarbamide treatment on organ dysfunction in children with SCD, showed that significantly elevated GFR was present at baseline in infants with a mean age of 13·7 months (Wang *et al*, 2011). This study used a robust, isotope-derived measurement of GFR, but the commonly derived creatinine-based estimates of GFR are much less accurate. Creatinine is a small molecule that is completely filtered by the glomerulus. It is also however, capable of being further secreted into the filtrate by the proximal tubule. Although this mechanism exists in normal individuals, it appears to be maximally utilized in those with SCD (Herrera *et al*, 2002). The subsequent clearance of creatinine from the blood is thus a function of both the glomerular filtration and the proximal tubular secretion of this molecule, making it an imperfect surrogate from which to

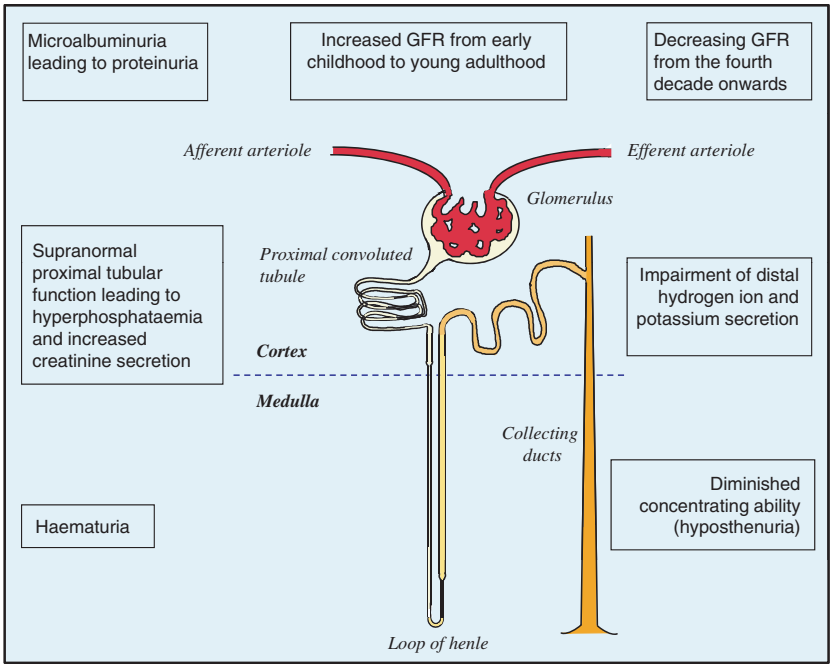

Fig 1. A representation of the renal nephron demonstrating the regions damaged in sickle cell disease leading to the clinical manifestations of sickle cell nephropathy. GFR, glomerular filtration rate.

estimate GFR. This tubular secretion however, is limited by the machinery available in the proximal tubule and is easily saturated and therefore cannot be implicated in the on-going rise in GFR that continues throughout childhood and early adulthood in affected individuals, often reaching 200 ml/min/1·73 m^2 or more. Other mechanisms that account for the rise in GFR include an increased cardiac output driven by anaemia, although this can only have a limited impact, as the rise in GFR is not reversed by repeated red cell transfusion (Statius van Eps *et al*, 1967). Localized prostaglandin release and an increase in nitric oxide synthase in response to hypoxia both result in an increase in renal blood flow in a similar manner to that described in early diabetic nephropathy. In contrast to this latter condition however, it is not associated with an increase in systemic blood pressure, as SCD patients tend to have a lower mean arterial pressure for age and ethnicity-matched controls (Thompson *et al*, 2007). Haem oxygenase-1 (HO-1) has also been demonstrated to be upregulated in injured kidneys (and indeed other tissues) in response to the ongoing haemolysis in SCD. HO-1 is responsible for the conversion of haem to biliverdin with the subsequent release of carbon monoxide (CO). Both biliverdin and CO at these levels are potent antioxidants and the CO acts locally as a vasorelaxant thus increasing both total renal blood flow and GFR (Nath *et al*, 2001; Nath, 2006).

It is not clear however, whether early or prolonged hyperfiltration is pathogenic in the aetiology of CKD. In a cross-sectional study of our own patient group, 51% of adults were found to have an estimated GFR (eGFR) ≥140 ml/min/1·73 m^2 (Sharpe CC and Thein SL, unpublished data), in keeping with that found by others (Haymann *et al*, 2010), making it one of the most common complications of SCD.

Hyperfiltration begins to disappear in the over-30 s, presumably as the nephropathy progresses. In a recent study of an elderly cohort of patients in Jamaica, 44% of people aged between 40 and 60 years demonstrated a >50% increase in their serum creatinine over time. In those who had died over the age of 60 years, chronic renal failure was sited as the major cause of death in 43% making it the most frequent fatal complication in this age group (Serjeant *et al*, 2009). Although this is circumstantial evidence, CKD due to SCN is preceded by hyperfiltration and proteinuria and hence these processes are likely to play a role in the pathogenesis of progressive renal dysfunction as they are thought to do in other renal diseases, such as diabetic nephropathy (Brenner *et al*, 1996; Magee *et al*, 2009).

Microalbuminuria and proteinuria

The appearance of albumin in the urine at levels above those detected in normal individuals is another early manifestation of SCN and begins to become apparent in some patients from late childhood. Unlike hyperfiltration, the prevalence of micro or macroalbuminuria continues to increase with age and heralds the onset of established SCN. In our own cohort, microalbuminuria (defined as a urinary albumin:creatinine ratio of ≥4·5 mg/mmol) is detectable in approximately 30% in the 15–23 age group, 40% in the 23–35 s and >60% in the over 35 s (Sharpe CC and Thein SL, unpublished data). Microalbuminuria can develop into frank proteinuria (protein:creat-

inine ratio (PCR) >50 mg/mmol) reaching the nephrotic range (>3 g total protein/24 h) in some. Full blown nephrotic syndrome is rare at about 4% but is associated with a very poor renal prognosis (Bakir *et al*, 1987). One rare but recognized cause of acute-onset nephrotic syndrome, which has been described in patients with SCD, is that associated with human parvovirus B19 (HPV B19) infection. Although widespread in the community, this usually benign infection becomes manifest in those with SCD as it often causes acute and self-limiting red cell aplasia. There have been a number of reports in which this acute infection has been followed within 2–3 months with acute nephrotic syndrome. In some of the cases that have been biopsied early, the collapsing variant of FSGS has been found (with or without evidence of direct HPV B19 infection) which is the classical lesion associated with virus-induced glomerulopathy (Wierenga *et al*, 1995; Quek *et al*, 2010). Although the acute features of nephrotic syndrome are self-limiting within a few months, the sequelae of the infection are worsening glomerulosclerosis, tubulointerstitial fibrosis and progressive renal dysfunction.

Tubular abnormalities

Hyposthenuria (inability to concentrate urine under conditions of water deprivation) is a phenomenon that is almost universal in people with SCD and also occurs in older people with sickle cell trait (SCT) (de Jong & Statius van Eps, 1985). It often leads to enuresis in children and can cause marked dehydration. Although not fully understood, it is linked to the increased renal blood flow in SCD that is apparent from early childhood and which affects more than just the GFR. In fact, the effect on GFR is disproportionately low when compared to total renal blood flow and hence the flow of blood to the interstitium is raised by a greater degree than that to the glomeruli (Guasch *et al*, 1997). This is mediated primarily by intra-renal prostaglandin release, which preferentially dilates the vessels of the inner medulla (de Jong & Statius van Eps, 1985), the region of the kidney responsible for urinary concentration. However, an increased blood flow to the medullary interstitium causes enhanced clearance of interstitial solute and a washout of the osmotic gradient, thus limiting the concentrating ability of the collecting ducts (Hatch *et al*, 1967). In addition, the increased delivery of salt and water in the tubular filtrate secondary to the high GFR, and intermittent hypoxia caused by sickling in the microvasculature, lead to local endothelin-1 (ET-1) release. ET-1 is not only a potent vasoconstrictor but also has marked naturetic and diuretic effects through stimulation of ET type b receptors in the renal collecting ducts, which leads to increased salt and water loss (Nakano & Pollock, 2011). Until the age of about 10 years, hyposthenuria is reversible by blood transfusion, thus indicating its pathophysiology is essentially functional through locally produced mediators. With time however, hyposthenuria becomes irreversible and is associated with a permanently damaged microvasculature with abnormally distended outer medullary capillaries and blind-ending inner medullary vasa recta (Statius van Eps *et al*, 1967, 1970a,b).

SCD is also associated with both proximal and distal tubular abnormalities. The increase in sodium and water loss from the collecting ducts leads to a reactive increase in sodium and water reabsorption by the proximal tubule. The reabsorption of sodium is the driving force for the reabsorption of other solutes, such as phosphate and β2-microglobulin, and hence many patients have hyperphosphataemia. Other solutes have a marked increase in proximal tubular secretion, such as creatinine and uric acid. Up to 30% of the total creatinine excretion can arise from tubular secretion and hence creatinine-based measurements of GFR can significantly overestimate renal function. An alternative endogenously produced molecule from which to estimate GFR is cystatin C, a 13 kDa non-glycosylated single chain protein produced by all nucleated cells. It is freely filtered in the glomeruli, completely absorbed and broken down by proximal tubular cells and the plasma concentration increases reciprocally with reduction in GFR. Estimations of GFR based on serum cystatin C correlate well with isotopically-measured GFR even when both the GFR and total renal plasma flow are elevated (Huang *et al*, 2011). Cystatin C has also been demonstrated to be a more accurate surrogate marker of renal function in both adults and children with SCD and hence its use is more likely to detect early decline in renal function (Marouf *et al*, 2006; Voskaridou *et al*, 2006).

Distal tubule function is often impaired leading to reduced potassium and hydrogen ion excretion and an incomplete renal tubular acidosis type IV. Hydrogen ion excretion is dependent upon the ability of the distal nephron to maintain an adequate hydrogen ion gradient between its basolateral and luminal aspect, a process which is energy-, and hence, oxygen-dependent. This defect is not usually apparent in those with normal renal function unless they are exposed to an acid load but becomes more problematic in patients with deteriorating renal function who can become disproportionately acidotic and hyperkalaemic. In most patients the potassium abnormality is associated with a normally functioning renin/angiotensin/aldosterone pathway but a few patients have been shown to have hyporeninaemic hypoaldosteronism (Oster *et al*, 1976; DeFronzo *et al*, 1979; Batlle *et al*, 1982).

Haematuria

Haematuria is common both in SCD and SCT. It can range from microscopic and painless, through visible and painless to visible and painful. It is usually self-limiting but can be severe enough to require transfusion. Small microinfarcts are often the cause of minor bleeding but full renal papillary necrosis (RPN) with sloughing of the ischaemic papilla can lead to severe haemorrhage and obstruction and may be complicated by superadded infection. The renal papillae are dependent upon the vasa recta for their blood supply and are therefore

Table II. Recommended investigations for patients with haematuria.

Renal tract ultrasound scan
Urine cytology
Computerized tomography urogram
Immunology for lupus nephritis
Autoantibodies
Double-stranded DNA antibodies
Complement levels
Consider cystoscopy
Consider renal biopsy if haematuria is present in combination with proteinuria and the above investigations are negative

particularly susceptible to ischaemic insults due to localized sickling. RPN can sometimes be diagnosed by ultrasonography but computerized tomography (CT) urography (or intravenous urography if CT is unavailable) and direct ureterorenoscopy have a much higher diagnostic rate (Jung *et al*, 2006; Kiryluk *et al*, 2007; Scheinman, 2009). Due to its self-limiting nature, the management of haematuria is usually conservative and limited to good hydration, pain relief and antibiotics if necessary.

Although most cases of haematuria are self-limiting it is important that they are investigated to exclude more sinister underlying causes (Table II). Renal stones, along with transitional cell carcinomas and renal clear cell carcinomas, may occur in the older patient group and must be excluded. One rare but devastating complication of both SCD and more commonly SCT is medullary carcinoma, a cancer specific to patients with sickle haemoglobinopathies. It is a highly aggressive cancer that can occur in children as young as 2 years of age. It is most often metastatic at presentation and although it may initially respond to chemotherapy, it has so far proven to be universally fatal within 2 years of presentation (Baig *et al*, 2006; Walsh *et al*, 2010).

Genetic modifiers

In keeping with other complications, renal dysfunction is relatively more common and more severe in those with HbSS and HbSβ^0 thalassaemia genotypes (sickle cell anaemia, SCA) than in those with HbSC or HbSβ^+ thalassaemia, which are generally milder forms of SCD (Platt *et al*, 1994; Guasch *et al*, 2006). However, from an individual's perspective there are few indicators that mark out those who will develop this complication and at what age. Renal dysfunction in SCD is affected by the two major genetic modifiers of SCD – HbF levels and α globin genotype –as part of the global effect on disease severity. Patients with the lowest HbF levels are more likely to develop renal failure and other vaso-occlusive complications. In keeping with this concept, patients with the Central African Republic (CAR) β^S haplotype are at an increased risk of developing renal dysfunction, presumably related to the lower HbF levels associated with the β^S CAR haplotype (Powars *et al*, 1991). In their cohort of 725 patients with HbSS, Powars *et al* (1991) also observed that no patient with elevated HbF level of >20% had renal insufficiency. The ability to produce HbF is mainly genetically controlled with three loci – *Xmn*1-$^G\gamma$ site in *HBB* cluster, *HBS1L-MYB* intergenic region on chromosome 6, and *BCL11A* on chromosome 2 – accounting for up to 50% of the HbF variance in adults (Thein & Menzel, 2009). Co-inheritance of α-thalassaemia, present in approximately 30% of SCD patients of African descent, reduces intracellular HbS concentration, red cell volume and reduced haemolysis (Ballas, 2001). The ensuing reduction in haemolysis has a protective effect on sickle complications ascribed to NO-depleted vasculopathy, such as pulmonary hypertension. Indeed, several studies have shown that coexisting α-thalassaemia in SCD delays the onset of microalbuminuria. A combination of candidate gene and genome-wide association studies (GWAS), focusing on different sub-phenotypes of SCD has identified a number of single nucleotide polymorphisms (SNPs) (Thein, 2008; Sebastiani *et al*, 2010). Using estimated GFR as a marker of renal function, SNPs in the *TGFB/BMP* pathway have been implicated in SCN (Nolan *et al*, 2007). The *TGFB/BMP* pathway is known to be a driver of many causes of CKD including diabetic nephropathy, which has many features in common with SCN.

Although not specifically related to SCD, the prevalence of CKD *per se* is recognized to be 2·5–5 times greater in people of African ancestry (Roderick *et al*, 1996; Palmer Alves & Lewis, 2010). Genetic association studies in this area have begun to reveal a number of genetic variants (SNPs) associated with an increased risk of developing kidney disease secondary to conditions such as diabetes, hypertension and HIV. Two genes in particular have been identified as having SNPs associated with CKD: *MYH9* and *APOL1* (Freedman *et al*, 2009a,b,c; Genovese *et al*, 2010; Kopp *et al*, 2010). If these SNPs represent true kidney disease-susceptibility factors and have a high prevalence in the genetic makeup of those ethnic groups that also carry the burden of SCD, then it is possible that co-inheritance could also lead to an increased likelihood of developing SCN.

Prevention and treatment strategies for SCN

Without direct evidence of specific susceptibility genes or causative environmental factors, delaying the onset of SCN comes down to a combination of generic measures for ameliorating SCD and its complications and those interventions that we know to be beneficial in slowing the progression of CKD due to other causes.

Therapies for treating SCD

Red cell transfusion, either intermittent or regular, has long been used for treating patients with acute and chronic complications of SCD including stroke prevention and pulmonary hypertension. There is little evidence on the benefits of long-term blood transfusions for prevention of renal complications. A retrospective analysis of 120 children

with sickle haemoglobinopathies concluded that chronic transfusion protected against the onset of microalbuminuria when commenced before the age of 9 years (Alvarez *et al*, 2006). However, another study found no difference in the number of children receiving chronic transfusion when those with microalbuminuria were compared to those without (Becton *et al*, 2010). As it is recognized that chronic transfusion can cause significant long-term complications, such as iron overload, infection with blood-borne viruses and alloimmunization, substantial evidence needs to be demonstrated as to the benefit of this intervention before its use can be justified for the treatment or prevention of SCN.

Hydroxycarbamide (HC) is currently the only agent approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of SCD. Clinical benefits include lower rates of pain, acute chest syndrome and need for blood transfusion. Long-term usage has been associated with improved growth and development in children (Ferster *et al*, 2001; Zimmerman *et al*, 2004; Hankins *et al*, 2005; de Montalembert *et al*, 2006) and reduced overall mortality and morbidity in adults (Steinberg *et al*, 2003; Bakanay *et al*, 2005; Voskaridou *et al*, 2010). Some small early studies suggested that it may also be efficacious both in the treatment of children with established SCN and also in preventing its onset (Fitzhugh *et al*, 2005; Thornburg *et al*, 2009). Unfortunately, larger studies have not so far borne this out. The BABY HUG study was a phase III randomized, placebo-controlled, double-blind study designed to evaluate whether starting HC in infancy would protect against chronic organ damage, with the primary endpoints being differences in splenic and renal function. Infants aged between 9 and 17 months (average age 13·6 months) were randomly allocated to receive HC therapy at 20 mg/kg/d or placebo. One hundred and sixty-seven subjects completed the study and although they were able to demonstrate a marked reduction in vaso-occlusive crises and hospitalization episodes in the HC group, the primary end points were not achieved (Wang *et al*, 2011). Accurate GFRs were measured at recruitment using Technetium-99m diethylenetriaminepentaacetic acid (Tc-99mDTPA) renal clearance and these were repeated at study exit after 2 years. In both the HC and placebo groups, the GFRs had risen from a baseline mean of 125 ml/min/1·73 m^2 to 147 ml/min/1·73 m^2 and to 146 ml/min/1·73 m^2, respectively, suggesting that HC was no better than placebo at preventing the progression of hyperfiltration in these young children. It is possible however that this study population was too young or the duration of treatment was too short to establish a long-term beneficial impact of HC treatment on either the development or stabilisation of SCN and so further studies are indicated.

The only curative treatment currently available for SCD is allogeneic haematopoietic cell transplantation (HCT) and is usually reserved for children with major complications, such as stroke. Although it is probable that HCT recipients who have a good outcome are likely to be protected from developing SCN in future, most published studies exclude those with established renal disease from receiving this treatment (Bhatia & Walters, 2008). One study evaluating the use of HCT in 10 adults with SCD did include three patients with renal dysfunction. After an average of 30 months of follow up it was noted that the decline in renal function post-procedure did not exceed the slope before the transplantation. In other words, the treatment neither exacerbated nor ameliorated the progression of renal disease (Hsieh *et al*, 2009). From a different perspective, there have been case reports describing HCT as safe in adults with end-stage renal failure, suggesting that the presence of advanced SCN should not exclude patients from receiving this treatment if available (Horwitz *et al*, 2007).

Therapies for treating CKD

Although SCN *per se* is a rare condition, in its advanced form it shares many of the pathological features common to other causes of CKD that eventually progress to organ failure. Regardless of the initial injury, it is the degree of fibrosis and tubulointerstitial atrophy that best correlate with loss of renal function. Although no drugs currently exist that are specifically anti-fibrotic in this setting, there are some generic treatments that have been proven beneficial in slowing the rate of decline. The most studied intervention is the treatment of concurrent hypertension both in diabetic and in non-diabetic kidney disease (Schrier *et al*, 2002; Sarnak *et al*, 2005; Ritz *et al*, 2010). Indeed in diabetic nephropathy it appears that aggressive lowering of the systolic blood pressure even below conventional targets (i.e. to <110 mmHg) has additional beneficial effects both on the progression of diabetic nephropathy and on cardiovascular events (Schrier *et al*, 2002). Patients with SCD tend to have a lower systemic blood pressure for age than ethnicity-matched controls. It has also been shown that patients with SCD and high-normal blood pressure values (systolic BP 120–139 mmHg, diastolic BP 70–89 mmHg) have both higher serum creatinine levels and an increased risk of pulmonary hypertension when compared with SCD patients with lower blood pressures (Thompson *et al*, 2007; Gordeuk *et al*, 2008).

Proteinuria is recognized to be pathological in the progression of renal disease and reducing the degree of proteinuria with angiotensin-converting enzyme (ACE) inhibitors (ACEi) and/or angiotensin receptor type II blockers (ARB) has been shown to slow decline in renal function both in patients with diabetic and non-diabetic nephropathy [Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) 1997; Nakao *et al*, 2003]. Although studies designed to demonstrate a benefit of ACE inhibition in SCN have been small and short-term, the results have been positive in terms of reducing proteinuria and hyperfiltration (Aoki & Saad, 1995; Falk *et al*, 1992; McKie *et al*, 2007). As there is such good evidence from other studies of long-tem benefit in people with non-diabetic kidney disease, it seems logical to extend this understanding to SCN. Therefore the treatment of proteinuric SCN generally includes the use of drugs that block the renin-angiotensin system. Although there are no published guidelines on when to

introduce this form of therapy, in our own practice we generally recommend the introduction of an ACEi or ARB when a patient has a urinary protein/creatinine ratio persistently above 100 mg/μmol, similar to the cut-off point adopted in the proteinuria studies mentioned above. We have noticed an additional benefit reported by patients that when prescribed this medication they notice a reduction in the number of times they have to pass urine at night, presumably as a result of the reduction in GFR that these drugs impart.

Management of advanced CKD in SCD

Despite optimal treatment with adequate management of blood pressure and control of proteinuria, a proportion of patients with SCD will develop progressive kidney failure that will eventually necessitate the need for renal replacement therapy (RRT), though precisely how many is unclear. In a four-decade observational study, Powars *et al* (2005) reported a 4·2% ESRD rate in patients with HbSS disease and 2·4% in those with HbSC disease (Powars *et al*, 2005). However, if the Jamaican study of their over 60-year-olds is representative of the current state of affairs, ESRD is likely to become much more prevalent as our patients survive into old age (Serjeant *et al*, 2009).

As renal function declines, the ability of the kidney to synthesize erythropoietin (epo) also declines. Chronic anaemia and tissue hypoxia are strong drivers for epo synthesis, SCD patients with normal kidney function often have epo levels well-above the normal range (Ballas & Marcolina, 2000). Erythropoiesis-stimulating agents (ESAs) can be useful in combination with HC in patients who are intolerant of HC alone due to reticulocytopenia (Little *et al*, 2006). In patients who develop progressive renal dysfunction, their ability to produce adequate levels of endogenous epo begins to decline when their GFR falls below approximately 60 ml/min. Patients often require very high doses of ESAs, though Hb targets should be lower than in the general CKD population and should not exceed 100 g/l due to the increased risk of triggering vaso-occlusive crises. However, even at these higher doses most patients also become transfusion-dependent by the time they reach ESRD. In our experience, and that of others, it is often still beneficial to continue ESA therapy as this can prolong the interval between red cell transfusion and minimize the risks of iron overload without likelihood of developing an increase in vaso-occlusive crises (Little *et al*, 2006; Schettler & Wieland, 2009). It is important to bear in mind, however, that adequate iron stores need to be maintained to achieve maximum erythropoiesis. Intestinal losses of iron due to sub-clinical bleeding are significant in advanced CKD and absorption of oral iron is reduced. Intravenous iron supplementation is therefore imperative in patients on ESAs not receiving iron through regular transfusions (Besarab & Coyne, 2010). The problem in most populations, however, is the expense of treatment coupled with the unpredictability of response and unclear dosage.

RRT becomes necessary to sustain quality and quantity of life when the degree of renal function becomes inadequate to control reasonable fluid balance, serum potassium levels in a safe range, the symptoms of uremia or the onset of acidosis. The precise timing therefore can be difficult to predict accurately but the rate of decline of renal function is an important factor. In our experience, in patients who develop progressive renal dysfunction secondary to SCN, the rate of decline can be quite rapid once the GFR falls below 40 ml/min. It is important therefore to recognize that the need for RRT may be imminent and to prepare the patient in a timely fashion. Entering into regular dialysis is formidable for the uninitiated but the process can be made less stressful by appropriate education and timely planning of dialysis access, be it arterio-venous fistula formation or the insertion of a catheter for peritoneal dialysis. In this way, the commencement of RRT can be done in an elective manner in the outpatient setting. It is recognized that for all causes of end-stage renal disease, the prognosis is much improved for those who have been known to nephrology services prior to reaching end-stage when compared to patients who are admitted to hospital as an emergency who initially require RRT through temporary access (Lorenzo *et al*, 2004).

Studies specifically pertaining to ESRD secondary to SCN are few. Powars *et al* (1991) reported that ESRD heralded a very poor prognosis, as not only was the average age at diagnosis very young (23·1 years in those with HbSS and 49·9 years in those with HbSC) but the mean time to death after reaching ESRD was only 4 years despite being on haemodialysis. A similar finding was reported by Saxena *et al* (2004a) who retrospectively compared a group of 11 patients with SCD in Saudi Arabia to 192 patients with renal failure of other causes. Those with SCD suffered more infectious complications, and lived on average, for only 27 months after commencing RRT and were significantly younger when they died (31 years verses 47·8 years). An analysis of all patients commenced on RRT between 1992 and 1997 from the US Renal Data System demonstrated that not only was SCN an independent risk factor for death, worse even than diabetes, but patients with SCD were much less likely to receive a kidney transplant (Abbott *et al*, 2002).

Despite apparently many obstacles in the path to kidney transplantation, it does appear from the limited data available that this from of RRT offers the best outcome for patients with ESRD secondary to SCN (Saxena *et al*, 2004b). In the study reported by Abbott *et al* (2002), SCN ceased to be an independent risk factor for death after transplantation. Ojo *et al* (1999) similarly studied the US Renal Data system and identified 82 patients who had received a renal transplant for SCN. The 1-year acute rejection rate and graft survival were not significantly different in these patients when compared to ethnically-matched controls who received grafts for other causes of renal failure, though the 3-year graft survival was lower (48% vs. 60%) (Ojo *et al*, 1999). Scheinman (2009) also reported an analysis of the US data system and similarly

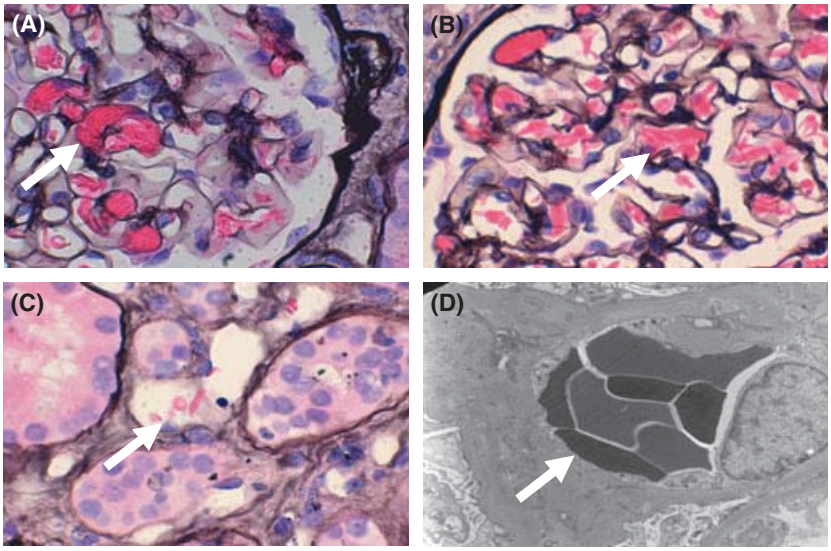

Fig 2. Histology of acute sickle nephropathy in a kidney transplant. (A and B) Sickled red blood cells (RBCs) within the capillaries of the glomerulus. (C) Sickled RBCs within peritubular capillaries. (A–C, original magnification ×400.). (D) An electron micrograph of a capillary occluded with sickled RBCs.

concluded that, although long-term graft and patient survival were not quite as good as for patients with other causes of renal failure, the prognosis for individuals with SCN was far better after transplantation, with a projected 7-year survival of 67% (vs. 83% for other African American) as opposed to a 10-year survival of only 14% for those who remained on dialysis. Warady and Sullivan (1998) reported a good outcome in nine paediatric patients treated with renal transplantation. In our single-centre experience, patients with SCD do wait longer on the transplant waiting list than ethnically and age-matched counterparts (2·79 years vs. 1·99 years, Sharpe CC, unpublished data) primarily due to intercurrent illness. However, the average time to death from commencing RRT is 9·5 years in those who are transplanted compared to 2·7 in those that remain on dialysis (Sharpe CC, unpublished data). This kind of information is clearly biased by the fact that only those fit for transplantation are offered this method of RRT but nonetheless encourages early recognition and preparation of patients for transplantation if needed.

Post-transplant management

One reason for graft loss is recurrence of SCN, both acutely in the peri-operative period and chronically. In our experience, patients with ESRD receiving RRT experience very few painful crises, probably as a result of relatively frequent blood transfusions. Following transplantation, we have witnessed a significant rise in the haemoglobin, even without ESA therapy and this has been accompanied by an increase in the number of painful crises experienced by the patients [(Breen & Macdougall, 1998; Chatterjee, 1980) Sharpe CC and Thein SL, unpublished data]. Acute intra-renal sickling has been demonstrated on biopsy by us and others as a cause for a sudden deterioration in renal function post-transplantation (Fig 2) (O'Rourke *et al*, 2008). This has also been described in a number of cases where the recipient has had sickle cell trait rather than SCD (Chatterjee *et al*, 1978; Kim *et al*, 2011). To minimize the risk of this complication occurring peri-operatively we recommend patients with SCD receive a simple top-up transfusion if very anaemic or red cell exchange with a view to reducing the HbS to <30% prior to transplantation. Although no evidence base exists, we feel it is reasonable to offer regular, preferably exchange, transfusion post-operatively to patients with either evidence of acute sickle nephropathy in their transplanted kidney or to those who have lost a graft previously to recurrent SCN. Some physicians would offer regular exchange transfusion post-operatively to all patients regardless, with a view to preserving function of the transplanted kidney,

Conclusion

SCN is a common and increasingly prevalent complication of SCD and much is to be learned about how to manage these patients in the optimum way. Close monitoring in the outpatient clinic with early detection and management of proteinuria and hypertension may well protect some patients from the need for RRT and further studies on the timing of this intervention are warranted. Certainly, patients with progressive SCN should ideally be managed in a joint sickle/renal setting. Large cohort studies on both adults and children with SCD will help to identify genetic and/or environmental risk factors that predispose patients to complications such as SCN. This will allow us to identify susceptible individuals before the onset of established disease, address any modifiable risk factors and refer them to nephrology services in a timely fashion.

Although there are no specific therapies for the management of SCN as yet, there are numerous potential treatments for SCD that may prove to be beneficial. As these gradually become available in the clinic, their impact on SCN and all the known sequelae of this complicated disease will need to be evaluated.

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