How we treat sickle hepatopathy and liver transplantation in adults

Kate Gardner\textsuperscript{1,2}, Abid Suddle\textsuperscript{3}, Pauline Kane\textsuperscript{4}, John O’Grady\textsuperscript{3}, Nigel Heaton\textsuperscript{3}, Adrian Bomford\textsuperscript{2}, and Swee Lay Thein\textsuperscript{1,2}

1. King’s College London School of Medicine, Molecular Haematology, Division of Cancer Studies, London SE5 9NU, UK
2. King’s College Hospital NHS Foundation Trust, Department of Haematological Medicine, Denmark Hill, London SE5 9RS, UK
3. King’s College Hospital NHS Foundation Trust, Institute of Liver Studies, Denmark Hill, London SE5 9RS, UK
4. King’s College Hospital NHS Foundation Trust, Department of Radiology, Denmark Hill, London SE5 9RS, UK

Correspondence: Swee Lay Thein
King’s College London School of Medicine
Molecular Haematology
The James Black Centre
125 Coldharbour Lane
London SE5 9NU, UK

Tel: +44 (0)20 7848 5443 / 5447
Fax: +44 (0)20 7848 5444

Email: sl.thein@kcl.ac.uk
Abstract

Sickle cell disease (SCD) has evolved into a debilitating disorder with emerging end-organ damage. One of the organs affected is the liver causing ‘sickle hepatopathy’ an umbrella term for a variety of acute and chronic pathologies. Prevalence of liver dysfunction in SCD is unknown, with estimates of 10%. Dominant etiologies include gallstones, hepatic sequestration, viral hepatitis and sickle cell intra-hepatic cholestasis (SCIC). In addition, causes of liver disease outside SCD must be identified and managed. SCIC is an uncommon, severe subtype, with outcome of its acute form vastly improved with exchange blood transfusion (EBT). In its chronic form, there is limited evidence for EBT programs as a therapeutic option. Liver transplantation may have a role in a subset of patients with minimal SCD-related other organ damage. In the transplantation setting, EBT is important to maintain a low hemoglobin S fraction peri- and post-transplantation. Liver dysfunction in SCD is likely to escalate as lifespan increases, and patients incur incremental transfusional iron overload. Future work must concentrate not only on investigating the underlying pathogenesis, but also identifying in whom and when to intervene with the two treatment modalities available: EBT and liver transplantation.
Case Presentation

A black British man of African-Caribbean descent was diagnosed with sickle cell disease (SCD, genotype HbSS) as a child, and followed up in our institution. His medical history comprised common complications of SCD: gallstones followed by laparoscopic cholecystectomy, priapism and multiple admissions with acute pain crises. He was reluctant and irregular in taking hydroxyurea. He had no history of alcohol excess and his body mass index was normal.

He developed abnormal steady-state liver function at age 23 years, with hyperbilirubinemia which peaked over 500µmol/l (30mg/dl, 68% conjugated bilirubin) during an acute hospital admission. This was followed by recurrent admissions each characterized by right upper quadrant abdominal pain, fever and acute worsening of liver enzymes, accompanied by extreme hyperbilirubinemia. A laparoscopic cholecystectomy at age 25 years did not improve symptoms. A regular program of simple (additive) blood transfusions was initiated in an attempt to control the frequency of acute pain and a presumed diagnosis of sickle cell intra-hepatic cholestasis (SCIC).

Further liver investigations showed no other obvious cause for liver disease: liver imaging and abdominal CT demonstrated hepatomegaly with right and left intra-hepatic duct dilatation, suggestive of a cholangiopathy, a normally-enhancing liver and patent vessels; laboratory results revealed negative autoimmune screen, normal α-feto-protein levels, and negative viral serology (for Hepatitis B, Hepatitis C, Hepatitis A, HIV). Ferritin levels in steady state were markedly raised at 3,000-4,000µg/l. An R2-MRI liver showed a liver iron concentration of 7.9mg Fe/g DW consistent with transfusion-related iron overload. At this stage, he has had a lifetime red cell transfusion of 796 units, the large majority being exchange units to maintain an HbS% target of <30-40%. His bilirubin and liver enzymes continued to increase despite the supportive treatment, although there was no evidence of impaired hepatic synthetic function.

In early 2011, aged 32 years, he developed decompensated liver failure with portal hypertension, ascites and impaired synthetic function (See Figure 1A for CT liver with contrast). At this stage, evaluation of other vital organs revealed, at worse, only mildly impaired function (echocardiogram with left ventricular ejection fraction 58% and normal tricuspid regurgitant jet velocities; mild reduction in pulmonary function testing, FEV 67% predicted, FVC 65% predicted; no evidence of sickle lung disease on chest computed tomography; mildly reduced creatinine clearance on 24 hour urinary testing at 50mls/min). He underwent formal hepatological assessment for liver transplantation (LT) using the standard protocol; his United Kingdom End-Stage Liver Disease (UKELD) score was 61 which indicated a 50% chance of 1-year survival. The situation was that of an uncommon
hepatological complication of a common hematological condition. We should emphasize that end-stage chronic liver disease in SCD is not an accepted indication for LT in the United Kingdom. His case was accepted on appeal to the National Appeals Committee.

He underwent liver transplantation on 15 July 2011, aged 33 years. Post-operatively, he developed metabolic acidosis which was corrected with hemofiltration, and a paralytic ileus that improved spontaneously. He was also treated for an Escherichia coli bacteremia. The explanted liver was nodular and weighed 3700 grams (Figure 1B); histology demonstrated liver cirrhosis with predominant sclerosing cholangitis, moderate siderosis, sickle cells in sinusoids, and a biliary abscess.

After transplantation, his liver enzymes normalized within one month while being maintained on an exchange blood transfusion (EBT) program (Figure 1C). Immunosuppression was maintained with steroids and tacrolimus. Sickle-related complications after transplantation included: two admissions with sepsis; proteinuria treated with candesartan; and priapism. Intractable priapism was not seen pre-transplant, and may be related to the return of normal liver function and sex hormone synthesis. His priapism did not respond to Etilefrine; hydroxyurea therapy was re-initiated but again, he was non-compliant. His priapism was eventually controlled by increasing the frequency of EBT (maintaining HbS% <30%) to 4-weekly intervals and his serum ferritin has normalized. Currently, he has had a lifetime exposure to over 1200 red cell units, although he has not developed any detectable red cell allo-antibodies. Two years after his LT, he fathered another child.

Discussion

How do we define “sickle hepatopathy”? In developed countries, SCD has evolved into a debilitating chronic disorder with significant morbidity due to end-organ damage. The liver is one of the affected organs, resulting in “sickle hepatopathy”. In SCD, some end-organ damage has a well-recognized natural history with identified treatments: proteinuria and renal impairment; right sided heart pressures and pulmonary hypertension; and high velocities on trans-cranial Dopplers and ischemic stroke risk (in children). However, the nature of liver dysfunction in SCD has not been characterized, nor has the natural history and pathogenesis of the liver disease been fully defined. This lack of knowledge prevents specific monitoring, and deciding when, how and in whom to intervene.

“Sickle hepatopathy” is an umbrella term covering a wide variety of pathologies, both acute and chronic, which occur as a consequence of the sickling process including gallstone disease, hypoxic
liver injury, hepatic sequestration, venous outflow obstruction, viral hepatitis (especially in the multi-transfused patient), hepatic crises, and SCIC.\(^{(1)}\) Some clinicians, however, consider sickle hepatopathy as a term reserved for intrahepatic cholestasis.\(^{(2,3)}\) The clinico-pathological features are aggravated by liver iron overload that results from cumulative red cell transfusions. It is important to look for additional causes of liver disease; in the 2007 King’s College Hospital cohort, \(^{(1)}\) 37% had a second liver co-morbidity, including autoimmune liver disease and viral hepatitis. Diagnosis is confounded by problems encountered with obtaining liver tissue for histological analysis; SCD has been suggested to be a contra-indication to liver biopsy in the acute setting.\(^{(4)}\)

SCIC is an uncommon but severe form of sickle hepatopathy, first described in 1953.\(^{(5)}\) Clinically, it comprises severe right upper quadrant pain, acute hepatomegaly, coagulopathy, extreme hyperbilirubinemia (mainly conjugated in contrast to the typical unconjugated hyperbilirubinemia seen in hemolytic anemias) but moderately elevated liver enzymes, with occasional progression to acute hepatic failure. Pathologically, it involves sickling within hepatic sinusoids leading to vascular stasis and localized hypoxia. The hypoxic injury results in ballooning of the hepatocytes causing a direct back pressure effect, with resultant intra-canaliculicular cholestasis, its defining feature.\(^{(6)}\) SCIC is most commonly described in its acute form, sometimes presenting as recurrent episodes, and in a subset becoming chronic, eventually evolving into progressive liver failure. This contrasts with the pediatric experience, where cases of extreme hyperbilirubinemia with intrahepatic sickling have been reported to recover spontaneously with supportive care alone. \(^{(2,3)}\)

**How common is liver dysfunction in SCD?**

As liver dysfunction in SCD is difficult to define, its prevalence too is difficult to document, with previous reports of around 10%.\(^{(7)}\) Using liver function tests to assess liver damage in SCD is confounded by abnormal liver enzymes reflecting not only intrinsic liver disease but also hemolysis. Our experience reveals that patients with SCD have evidence of disrupted liver synthetic function late in the natural history. Our patient developed abnormal coagulopathy and hypoalbuminemia in March 2011, nine years after he first developed hyperbilirubinemia. Thus, abnormal liver enzymes should prompt a more comprehensive liver workup including laboratory and radiological assessments, aimed at identifying true liver dysfunction, and determining severity and etiology.

As well as looking for causes of liver dysfunction unrelated to SCD, an assessment of iron overload must also be made, especially in view of the increasing use of blood transfusion in SCD.\(^{(8)}\) The risk of hepatic siderosis is further likely to escalate with the increasing lifespan in SCD patients and cumulative exposure to transfused red cells.
What is appropriate management of "sickle hepatopathy"?

The management of “sickle hepatopathy” relies on accurate identification and treatment of any co-existing cause(s). The diverse etiologies contribute to the extensive variation in natural history and severity of liver disease. Joint management involving a hepatologist with an interest in SCD is useful.

Investigation

It is important to exclude other causes of liver dysfunction in SCD including alcohol, medication (including recreational drugs) and BMI evaluation (see table 1).

In any liver disease, the first imaging investigation is an abdominal ultrasound (USS), the technique is accurate in assessment of the presence of cirrhosis, ascites, portal vein anatomy, biliary calculi and biliary dilatation. Ultrasound is also the most sensitive imaging technique for assessment of acute calculous cholecystitis with a positive predictive value of 95% when gallbladder wall thickening is more than 3.5mm and gallstones are present. Abdominal CT is useful in diagnosing complications of biliary disease, perforation, emphysematous cholecystitis, cholangitis and liver abscess. Magnetic resonance cholangiopancreatography (MRCP) is the imaging technique of choice in the diagnosis of cholangiopathy; it is non-invasive, accurate and predicts the need for endoscopic retrograde cholangiopancreatography (ERCP) to allow intervention regarding common bile duct calculi and dominant stricture. The accuracy of MRCP for detecting biliary calculi is 98%.\(^{(9)}\) MRCP is comparable with ERCP for the diagnosis of primary sclerosing cholangitis but less effective in diagnosis of dominant strictures.\(^{(10)}\)

Using ferritin as a marker of iron burden in SCD is complicated by ferritin itself being increased in both liver disease and inflammation. Baseline magnetic resonance imaging, such as R2MRI measurements, is recommended to detect liver iron load.

Liver biopsy is a relative contra-indication due to the high risk of bleeding and liver rupture. We recommend that it is only performed after specialist hepatology assessment and when results will significantly influence management; such as with a diagnostic dilemma, for example with intrahepatic cholestasis and autoimmune disease in the differential diagnosis. If a liver biopsy is conducted, a trans-jugular route is recommended.
Treatment options of specific complications
Iron chelation for iron overload is recommended. Quantitatively, chelation is considered appropriate when liver iron concentration exceeds 7 mg Fe/g DW, roughly equivalent to transfusion of more than 20 units red cells.

The role of elective cholecystectomy for asymptomatic cholelithiasis remains controversial. For example, in a recent longitudinal study of 26 pediatric SCD patients with radiological evidence of cholelithiasis, 25 remained asymptomatic over a 13 year follow up period. In contrast, in a 2007 Italian series of 30 pediatric patients, significantly increased morbidity was reported in patients who were not electively cholecystectomized and who subsequently proceeded to symptomatic cholecystectomy. It is also debatable if patients who have co-inherited Gilbert’s syndrome (polymorphism in promoter region of UGT1A gene) and thus genetically predisposed to further increases in serum bilirubin levels, and gallstones, should have elective cholecystectomy.

In early reports of SCIC, mortality was high, caused by fulminant hepatic failure or bleeding. Outcome has since improved dramatically with EBT (first described by Sheehy in 1980). EBT rather than simple blood transfusion is recommended for managing both acute and chronic SCIC for ease of achieving HbS% target and to reduce the risk of secondary iron overload. Early implementation of an EBT program is critical; suggested thresholds of HbS% have been reported as <20 and <30%.

In cholestasis, use of the bile acid, ursodeoxycholic acid, can improve biliary flow where sludging is a feature. Hydroxyurea, beneficial in patients with frequent painful crises and acute chest syndrome, has not been shown to reduce the frequency of hepatic sequestration crises. Further work is needed on exploring the preventative effects of hydroxyurea on organ damage including sickle hepatopathy, especially SCIC.

When do we intervene?
In general, assessment of the severity of liver disease and likely predominant etiology(ies) can be made after clinical assessment and appropriate laboratory and radiological investigation. In the severe acute liver dysfunction syndromes, and progressive liver cholestasis, anecdotal experience is accruing for the use of EBT although this has not been rigorously scrutinized. There are several case reports demonstrating that acute SCIC can be reversed with prompt EBT. With progressive disease, it is not clear when EBT should be commenced or what the aims of treatment should be. In addition to our patient, there are two examples in the literature of the use of a program of EBT to manage chronic SCIC in the non-transplant setting. Maintaining HbS levels at less than 20-30% has been proposed, but again this is based on pragmatism rather than evidence. Future work
must explore the natural history of SCIC in order to identify which patients are at risk of disease progression and who would benefit from regular EBT. We suggest a pragmatic schema (Figure 2) for managing those with "sickle hepatopathy".

**Are there any predisposing factors?**

Patients with “sickle hepatopathy” frequently have multiple causes of liver disease. Whether these are independent pathological processes or represent a predisposing factor to SCIC is unknown; the pathogenesis of SCIC is not clear. What we do note is the high prevalence of gallstone disease which may represent a predisposing factor to intrahepatic cholestasis prompting elective choleystectomy for asymptomatic cholelithiasis. We further note in the documented cases of SCIC, there is a gender disparity in disease incidence, with only 26% female. In SCD, transfusional iron overload is linked with liver fibrosis. It is likely that non-transferrin bound iron induces reactive oxygen species which not only directly causes cellular damage but also depletes nitric oxide levels leading to endothelial dysfunction. These additional pathologies are likely to contribute to the disease process of SCIC and therefore represent “predisposing factors” but they could also represent coincidental diagnoses; either way, it is important to make an early diagnosis and management of other hepatic/biliary complications in SCD.

**What is the role of liver transplantation?**

World-wide experience of liver transplantation as a therapeutic modality for end stage liver disease as a consequence of sickle hepatopathy is slowly developing, with 22 cases reported in the literature. However, several questions remain unanswered. The poor results reported in early case series have improved, to some degree, in later studies. This is likely a consequence of better patient selection and improved peri-operative management of SCD.

What can be extrapolated from the data? Good vital organ function is crucial for LT surgery itself; this precludes many SCD patients who have already developed significant sickle-related complications of the heart, lungs, kidneys and brain, concomitant with their “sickle hepatopathy”. Two clinical phenotypes that benefit most from liver transplantation can be identified: one with end stage liver disease due to SCD, but without significant sickle-related damage of other organs, and the second is those with liver disease co-incident to SCD (for example auto-immune liver disease) who perhaps have a milder SCD phenotype. Specific transplant-related complications in patients with SCD include vascular thrombosis, an increased incidence of sepsis and neurologic dysfunction. Recurrent sickle hepatopathy in the liver graft has been reported. Recommendations for peri-operative management of SCD include regular EBT to maintain HbS fraction <30%, again this is not evidence based and largely extrapolated from studies involving non-transplant surgery, and primary and secondary
stroke prevention.\(^{39-40}\) One should also note the variable outcomes of LT in the acute setting; there is a high incidence of failure of the liver graft and poor patient survival.\(^{27-30,34,36}\)

Currently, end stage liver disease as a consequence of sickle hepatopathy is not an accepted indication for liver transplantation in the United Kingdom. A pilot study is underway to define the role of this treatment modality in this group of patients. We would recommend that patients approaching end stage liver disease are referred to centers where joint hematological and hepatological assessment can be performed and patients offered the full range of treatment options.

Our experience in the UK represents a well-resourced setting with well-established infrastructure within hematology and hepatology. Liver transplantation is a difficult option for those in poorly resourced settings. Transplantation planning must not merely take account of the workup and surgery itself, but also consider post-operative multi-disciplinary care involving hematology and EBT, and the logistics and side effects of immunosuppression.

**Conclusion**

“Sickle hepatopathy” is a non-specific term reflecting the heterogeneity of liver dysfunction in SCD. It is important to look for, and treat a cause of liver disease outside SCD itself. Data from our cohort suggest that hepatitis C and alcohol as a cause appear lower than reports from elsewhere. Being able to predict who will progress to end stage liver disease remains an elusive goal. Medical managements are limited and not evidence-based; there is an urgent need to formally evaluate the therapeutic strategies of EBT and liver transplantation. Regular EBT should be considered for patients with severe acute hepatic crises and progressive cholestasis. Liver transplantation may have a role in a sub-set of patients. A current trial is exploring the possibility of reduced intensity hematopoietic stem cell transplantation in SCD with end-organ damage, but whether this could reverse liver damage is unknown (http://clinicaltrials.gov/ct2/show/NCT01950429). Finally, we anticipate that liver dysfunction will become an increasing problem in an aging SCD population, with more aggressive transfusion programs contributing to increased hepatic siderosis.
Acknowledgements
We thank Claire Steward for help in preparation of the manuscript.

Authorship
KG, AS, PK, AB and SLT wrote the manuscript; all authors reviewed and commented on the manuscript.

Conflict of interest
The authors have declared that no conflict of interest exists.
References


Table Legend

Table 1: Investigations for causes of sickle hepatopathy in SCD
Table 1: Investigations for causes of sickle hepatopathy in SCD

- Clinical history and examination
  - Alcohol history
  - BMI
  - Drug history

- Imaging
  - Liver USS including assessment of vessel patency, and biliary system
  - Other imaging: CT abdomen, MRCP, ERCP

- Laboratory
  - Viral serology: Hepatitis B, Hepatitis C, HIV, CMV, EBV, Hepatitis A
  - Autoimmune screen: antinuclear antibody, anti-smooth muscle antibody, liver/kidney antibody, anti-soluble liver antigen, anti-mitochondrial antibody
  - α-feto-protein levels
  - Ceruloplasmin
  - Alpha 1-antitrypsin

- Liver biopsy
  - Usually not indicated unless genuine diagnostic dilemma

- Iron status
  - Ferritin
  - Magnetic Resonance Imaging for liver iron concentration
Figure Legend

Figure 1A: CT liver with contrast pre-transplant.
CT abdomen with intravenous contrast in July 2011 (just prior to transplant) demonstrated longstanding changes including: a nodular liver with left lobe hypertrophy, biliary dilatation, varices (splenic, umbilical and retroperitoneal), and moderate ascites. A low density area in liver segment 3 (probable biliary abscess) was also noted.

Figure 1B: Explanted liver

Figure 1C: HbS% post-transplant, peri-transplant and post-transplant

Figure 2: Management pathway for “sickle hepatopathy”
Hyperbilirubinemia: Bili >200μmol/L or >12mg/dl

Exclude (a) hyperhemolysis and (b) evidence of other liver disease (see table 1)

Predominantly conjugated hyperbilirubinemia, with minimal liver damage

First episode of SCIC
- Consider EBT

Recurrence of acute SCIC
- Consider regular EBT program

Progressive hepatopathy (continuing SCIC)
- EBT program
- Evaluate other organ damage & consider LT suitability

Note 1 – Exercise caution in bilirubin interpretation in those with concomitant Gilbert’s syndrome or G6PD deficiency
Note 2 - At any stage: fulminant liver failure: for hepatology lead +/- consideration of LT dependent on patient and vital organ function
Note 3 – For patients with non-SCD causes (e.g. autoimmune hepatitis) and refractory/progressive to treatment of the primary cause, consider a regular EBT program
Note 4 – Pay particular attention to monitoring of, and management of, iron overload in these patients where hepatic siderosis may exacerbate other causes of hepatic dysfunction
Note 5 – Liver biopsy not indicated unless a genuine diagnostic dilemma
Note 6 – Ursodeoxycholic acid may be considered for cholestasis to improve biliary sludging

Gardner et al, Figure 2
How we treat sickle hepatopathy and liver transplantation in adults

Kate Gardner, Abid Suddle, Pauline Kane, John O'Grady, Nigel Heaton, Adrian Bomford and Swee Lay Thein