Hepatic Dysfunction in Sickle Cell Disease: A New System of Classification Based on Global Assessment

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Background & Aims: **Hepatic dysfunction in adults with sickle cell disease varies in character and severity from self-limited cholestasis to life-threatening acute liver failure and cirrhosis. Because previous attempts to describe patterns of liver disease have not reflected clinical experience, we aimed to characterize the presentation, clinicopathologic findings, and natural history of such patients.** ***Methods:*** **We reviewed the clinical, laboratory, radiographic, and histologic features with the natural history of 38 patients (mean age, 33 years) with Hb SS, SC, or S-β thalassemia referred to a tertiary liver center for assessment.** ***Results:*** **Distinct disease patterns were identified that comprised massive hepatocellular necrosis (5%), acute severe sequestration and cholestasis in the context of sepsis (18%), cirrhosis (18%), chronic, fluctuating sequestration without cholestasis (21%), mechanical biliary obstruction (8%), siderosis without cirrhosis (8%), generalized cholangiopathy (8%), venous outflow obstruction (3%), and miscellaneous (11%). Of the 20 who required emergency admission, 8 did not survive their index admission, and 3 patients died during follow-up admissions (4 months–4 years later). There were 3 instances of hemorrhage related to liver biopsy. One patient underwent transplantation but died. Hematologic and biochemical markers did not discriminate well between survivors and nonsurvivors. The incidence of a second hepatic pathology (ie, viral hepatitis, autoimmune disease, transfusional siderosis) was 37% and was associated with the finding of more advanced histologic fibrosis.** ***Conclusions:*** **Patterns of hepatic dysfunction in sickle cell disease are diverse and demand clear characterization for each individual; however, groups with a poor prognosis can be identified after collation of clinical, laboratory, and radiologic data. Findings at biopsy (which is associated with higher risk of bleeding in this group) might be anticipated by noninvasive test results.**

Previous descriptions of hepatic dysfunction in sickle cell disease (SCD) have concentrated predominantly on acute manifestations. These include hepatic crisis that might accompany generalized vaso-occlusive crises; sequestration crisis, in which a large volume of blood becomes trapped in the liver, resulting in hypovolemia and profound anemia but with modest changes in liver function; and acute cholestasis, in which it is proposed that hepatocyte anoxia results in reduced bile formation and disturbance of bile flow within canaliculi.[1] Chronic hepatic dysfunction in SCD is less well-described. Mild abnormalities in liver function tests are seen in those with steady state disease,[2] and 32 of 130 consecutive, unselected patients with HbSS or HbSC were found to have significant dysfunction in one study.[3] However, overt and symptomatic clinical disease appears to be uncommon. An association with cirrhosis has long been suspected, and in one large series, 10% of liver biopsies demonstrated advanced fibrosis in the absence of any other etiologic explanation.[4]

The term *sickle hepatopathy* has been derived as a descriptor of liver dysfunction of both acute and chronic nature, yet it is limited by the fact that it does not accommodate variations in presentation and outcome. Attempts to further characterize hepatic dysfunction have demonstrated differences in severity according to age; in a review of published cases and a small additional cohort, those deemed to have less severe hepatic synthetic dysfunction were younger (11.8 years) and had lower mean bilirubin levels and better prognosis (4% mortality) than older patients (24.5 years), who exhibited greater derangements in liver function (64% mortality).[5] Although homozygous (Hb SS) patients appear to be affected most severely, compound heterozygote patients (ie, Hb SC, Hb S-β thalassemia) might also develop liver disease.

Histologic examination of liver biopsy specimens has also shed light on the pathogenesis of hepatic dysfunction. Vascular obstruction by sickle cells, sinusoidal expansion, and perisinusoidal fibrosis are the predominant lesions reported, although other investigators have reported predominant lesions as those of iron overload and chronic cholestastasis; the latter was attributed either to choledocholithiasis or viscous bile.[6,7] In other series, evidence of viral infection (hepatitis B or C) has been reported in between 20%–50% of biopsy series, usually as a consequence of blood transfusion.[7,8] Comparison of 19 antemortem and 32 postmortem samples from different patients raised the possibility of artifactual intrahepatic sickling after death or features caused by formaldehyde, although this is

Abbreviations used in this paper: AIH, autoimmune hepatitis; ANA, antinuclear antibody; CT, computed tomography scan; ERCP, endoscopic retrograde cholangiopancreatography; FNH, focal nodular hyperplasia; HTLV, human T-cell lymphotropic virus; LT, liver transplant; MRCP, magnetic resonance cholangiopancreatography; NRH, nodular regenerative hyperplasia; PSC, primary sclerosing cholangitis; SCD, sickle cell disease; SLE, systemic lupus erythematosus; SMA, smooth muscle antibody; USS, ultrasound scan.

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Table 1. Clinicopathologic Data for Subgroup With Acute Sequestration and Cholestasis

Patient no.	Age (*y*)	Acute/chronic	Sickle status	Cofactor	Presenting features
1	27	Ac	SS	—	Fever and jaundice
2	58	Ac	SC (α-thalassemia)	—	Fever and jaundice
3	50	Ac	SS	—	Painful crisis in association with pneumonia
4	32	Ac	SS (α-thalassemia)	—	Jaundice after recent anabolic steroids
5	39	Ac	SS	HCV	Jaundice and hepatomegaly; cocaine use
6	19	Ac	SS	HCV	Painful joints, rigors, jaundice
7	25	Ac	SS	HCV	Fever and jaundice

Ac, acute presentation; A, alive; D, dead; MOF, multiple organ failure; ARDS, acute respiratory distress syndrome.

controversial.[8] Further complicating the issue of liver biopsy, its relative value and safety have been questioned after several incidents of fatal bleeding after percutaneous approaches in patients with acute hepatic dysfunction.[9]

Regarding outcome, the literature is inconsistent. In a large study in which the circumstances surrounding the deaths of 209 adults with SCD were assessed by proportional-hazards regression, hepatic dysfunction (episodes of right upper quadrant syndrome, or raised bilirubin) did not appear to be associated with an increased risk of death, in contrast to renal dysfunction, episodes of acute chest syndrome, neurologic manifestations, or degree of anemia.[10] In contrast, a smaller multi-center analysis of causes of death in 53 SCD patients implicated cirrhosis in nearly one fifth of all deaths,[11] and in a recent single center analysis of 141 patients, 11.3% were identified as having died as a result of cirrhosis.[12] There therefore remains considerable doubt in terms of counseling and prognostication for SCD patients with either acute or chronic hepatic dysfunction. As a consequence of the inability to discriminate outcome according to clinical presentation, our aim was to identify patterns of liver disease in terms of presentation, clinical features, laboratory indices, and radiologic and histologic investigations in a cohort of patients carrying at least one sickle gene referred to a tertiary liver center.

Patients and Methods

Patients

Adult patients with Hb SS, Hb SC, and HbS-β thalassemia referred to the liver unit at Kings College Hospital between 1999–2005 were identified from a prospectively maintained database. Details concerning mode of presentation were obtained from the database and abstracted from case records, and results of hematologic, biochemical, radiologic, and histologic investigations performed at presentation were analyzed.

Radiologic Investigations

Ultrasound scan (USS) and computed tomography (CT) scan findings were recorded in terms of liver enlargement, alteration in shape, presence of parenchymal heterogeneity, focal lesions, bile duct dilatation, and diagnostic features of other disease processes if found. Cholangiographic findings, if obtained, were also recorded. Radiologic investigations were ordered by the supervising physician according to clinical presentation; CT scanning was performed if there was clinical or

Table 2. Clinicopathologic Data for Subgroup With Cirrhosis

Patient no.	Age (*y*)	Acute/chronic	Sickle status	Cofactor	Presenting features
8	17	Ac	SS	AIH	Jaundice
9	38	Ac	S-β thalassemia	—	Jaundice
10	38	Ac	SS	HBV, HTLV	Jaundice and hepatomegaly
11	38	Ac	SS	—	Fever and jaundice
12	33	Ch	SS	HCV	LT assessment
13	42	Ch	S-β thalassemia	AIH	CLD follow-up
14	20	Ch	SS	SLE	CLD follow-up

Ac, acute presentation; Ch, chronic presentation; A, alive; D, dead; CLD, chronic liver disease.