Autoimmune Liver Disease in Children with Sickle Cell Disease

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Objective To assess the incidence, clinical features, and outcome of autoimmune liver disease (AILD) in patients with sickle cell disease (SCD).

Study design Single center retrospective review of patients with SCD with AILD referred between 1999 and 2015.

Results Thirteen of 77 (17%) patients with SCD with hepatic dysfunction were diagnosed with AILD (median age 11, range, 3.4-16 years) with a female preponderance (77%). Acute hepatitis and insidious onset were the commonest presentations. Two patients (15%) presented with acute liver failure. In 2 patients (15%), parvovirus B19-induced transient red cell aplasia preceded the diagnosis of AILD. All patients were positive for antinuclear and/or smooth muscle autoantibodies. Six of 12 patients (50%) had cholangiopathy on cholangiogram suggesting autoimmune sclerosing cholangitis (ASC). Liver biopsy, performed in 11 patients without complications, showed interface hepatitis in 90%. Patients with AILD were treated with standard immunosuppression. After a median follow-up of 3.8 years (range, 0.2-14.3), 10 patients are alive (1 was transplanted 6.4 years after diagnosis); 2 are lost to follow-up; 1 died of subdural hemorrhage before starting treatment for AILD. Five (42%) achieved full and 4 (33%) partial biochemical remission. Ulcerative colitis, present in 4 patients (2 male patients, 3 with ASC) was diagnosed in 2 patients before and in 2 patients after the diagnosis of AILD.

Conclusions AILD is not uncommon in patients with SCD, affecting mainly female patients and responding satisfactorily to immunosuppressive treatment. Liver biopsy is helpful in confirming the diagnosis and can be safely performed in the absence of acute vaso-occlusive sickling episodes. Ulcerative colitis is common in the presence of ASC. *(J Pediatr 2017;189:79-85).*

Sickle-cell disease (SCD) is caused by an autosomal recessive mutation of the *HBB* (beta globin) gene leading to abnormality of β-globin chain, hemoglobin S (HbS), which polymerizes when deoxygenated, resulting in deformed and rigid erythrocytes. Sickling of the erythrocytes, as well as altered expression of adhesion molecules, which promote increased adhesiveness of the red cells to the endothelium,[1] lead to vaso-occlusion, vasculopathy, and hemolytic anemia, causing end-organ damage. SCD includes sickle cell anemia (HbSS), hemoglobin S combined with hemoglobin C (HbSC), hemoglobin S associated with ß thalassemia [HbS/β thalassemia]), and other less prevalent combined heterozygous conditions.[2,3]

Hepatic involvement in SCD is common and ranges in severity from biochemical liver dysfunction to fatal liver failure and includes acute hepatic vaso-occlusion, hepatic sequestration, and sickle cell intrahepatic cholestasis (also known as sickle cell hepatopathy). These result from recurrent ischemia of the liver, vasculopathy, oxidative stress and reperfusion injury, and hemolysis causing high bilirubin levels. Ensuing elevated bilirubin excretion predisposes to cholelithiasis, reported in 35%-57% of patients with SCD. In addition, liver dysfunction in SCD might be due to other hepatologic problems such as transfusion-related hemosiderosis, chronic viral hepatitis, and autoimmune liver disease (AILD).[4-6] Liver histology can provide

AIH	Autoimmune hepatitis
AIH-1	AIH type 1
AILD	Autoimmune liver disease
ALF	Acute liver failure
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ASC	Autoimmune sclerosing cholangitis
AST	Aspartate aminotransferase
AZA	Azathioprine
ERCP	Endoscopic retrograde cholangiopancreatography
IBD	Inflammatory bowel syndrome
INR	International normalized ratio
HbS	Hemoglobin S
MRCP	Magnetic resonance cholangiopancreatography
p-ANCA	Perinuclear pattern antineutrophil cytoplasmic antibody
SCD	Sickle cell disease
SMA	Smooth muscle antibody
UC	Ulcerative colitis

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information on the etiopathogenesis of hepatic dysfunction.[7-10] However, the safety of percutaneous liver biopsy has been questioned particularly during acute sickling complications.[11]

AILD has been reported as a rare complication in patients with SCD.[6-8,12] To the best of our knowledge, there have been only 7 children documented from 3 case reports so far.[13-15] AILD is a progressive liver disorder of unknown etiology with serologic autoimmune features, which includes 2 conditions, namely autoimmune hepatitis (AIH), and AIH-sclerosing cholangitis overlap syndrome (autoimmune sclerosing cholangitis, ASC). AILD is characterized by elevated serum aminotransferase levels, increased levels of IgG, positive circulating autoantibodies (antinuclear antibody [ANA], smooth muscle antibody [SMA], anti-liver kidney microsomal antibody type 1), and portal inflammation and interface hepatitis on histology. Patients with ASC also have cholangiopathy on biliary imaging. Clinical manifestations of AILD are indistinguishable from other liver conditions and could have a fluctuating course, resulting in delayed diagnosis. Patients can progress to acute liver failure requiring liver transplantation if left untreated. Immunosuppressive therapy is effective and should be initiated as soon as the diagnosis is made.[16] AILD is particularly difficult to diagnose in the presence of SCD, because of the pre-existing abnormalities in liver tests associated with SCD, and the tendency to attribute all symptoms to SCD. Because of the complexity of diagnosis and rarity of the association between AILD and SCD, the aim of the present study was to assess the incidence, clinical features, and outcome of AILD in children with SCD referred to our center.

Methods

A retrospective review was performed to identify all patients with SCD referred to King's College Hospital, the largest tertiary referral center for pediatric liver disease in the United Kingdom, between January 1999 and June 2015 and diagnosed with AILD. The demographic data, clinical features, biochemical measures, histologic and radiologic findings, management, and outcome were recorded. AILD was diagnosed in patients with elevated aminotransferases, hypergammaglobulinemia, positive autoantibodies, interface hepatitis with portal plasma cell infiltration on liver histology, in the absence of other known causes of liver disease. The diagnosis of AIH type 1 (AIH-1) and AIH type 2 was based on the autoantibody profile: positivity at a titer of ≥1:20 for ANA and/or SMA define AIH-1, whereas a titer ≥1:10 for anti-liver kidney microsomal antibody type 1 defines AIH type 2.[17,18] ASC was diagnosed in those with AIH and evidence of a cholangiopathy on cholangiogram and/or on histology.[15] Other causes of liver diseases such as viral hepatitis, Wilson disease, or alpha-1-antitrypsin deficiency were excluded.

Modes of presentation were classified into 4 categories: (1) acute hepatitis with nonspecific symptoms mimicking an acute viral hepatitis; (2) acute liver failure (ALF) defined by the presence of coagulopathy (prothrombin time ≥15 seconds or international normalized ratio [INR] ≥1.5 not correctable by parenteral vitamin K) in the presence of clinical hepatic encephalopathy, or a prothrombin time ≥20 seconds or INR ≥2.0 regardless of hepatic encephalopathy, in the absence of known evidence of chronic liver disease[19]; (3) insidious onset with progressive fatigue, relapsing jaundice, and weight loss for several months before diagnosis; and (4) complications of chronic liver disease, such as bleeding from portal hypertension. Medical history of SCD, including SCD genotype and severity, and transfusion history were recorded.

Abdominal ultrasound scan findings were recorded in term of liver parenchyma heterogeneity, focal lesions, bile duct dilatation, biliary tract obstruction because of cholelithiasis or choledocholithiasis, and presence of splenomegaly. Cholangiography was performed either by magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Sclerosing cholangitis was diagnosed in the presence of bile duct irregularity, focal dilatation, or stricturing. All cholangiograms were re-evaluated by a radiologist at our institution with expertise in hepatobiliary imaging blinded to patient's history.

Liver specimens were obtained either by percutaneous or transjugular route and were re-evaluated by an experienced pathologist blinded to patient's history. The biopsy specimens were assessed for histologic features of AIH including interface hepatitis, portal inflammation, and lobular activity as well as biliary features such as bile duct injury, cholestasis, and cholangitis. Modified Ishak score was applied to assess necro-inflammatory activity and Metavir score was used for fibrosis staging as follows: no fibrosis (stage 0); enlarged fibrotic portal tracts (stage 1); periportal fibrosis (stage 2); bridging fibrosis (stage 3); and cirrhosis (stage 4).[20] The presence of sinusoidal dilatation, sequestration of sickle cells, venous outflow obstruction, mechanical obstruction of biliary tree, and siderosis were also evaluated. Upper endoscopy and/or colonoscopy were performed to investigate for inflammatory bowel disease (IBD) in patients with gastrointestinal symptoms. The diagnosis of IBD was made based on endoscopic and histology findings.

Prednisolone (2 mg/kg/day; maximum 60 mg/day) was commenced once diagnosis of AILD was made and then gradually tapered in parallel to the decrease of aminotransferase levels over 6-8 weeks to maintenance dose of 0.1-0.2 mg/kg/day or 2.5-5 mg/day. Azathioprine (AZA) at 1-2 mg/kg/day was added if aminotransferase levels plateaued or increased to minimize steroid side effects. Mycophenolate mofetil at 20-40 mg/kg/day (maximum 2000 mg/day) was used in cases resistant to conventional treatment.[21] In addition to immunosuppression, all patients were treated with ursodeoxycholic acid at 15-20 mg/kg/day. Patients were considered in remission when clinically recovered with normalization of aminotransferase and IgG levels, and negative or very low (<1:20) auto-antibody titer. Partial remission was defined as improvement of aminotransferase levels to ≤twice upper limit normal. In the case of relapse, prednisolone 1-2 mg/kg/day (maximum 60 mg/day) was re-administered then gradually tapered according to biochemical and clinical response.[22] Sulfasalazine or mesalazine and corticosteroids were the mainstay of treatment for mild and moderate-to-severe ulcerative colitis, respectively. In terms of