Sickle cell hepatopathy: Diagnosis and treatment with exchange transfusion

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This paper discusses a patient presenting with hyperbilirubinemia and sickle cell disease. The literature is reviewed regarding sickle cell disease and liver involvement. Pertinent aspects of diagnosis and management are discussed.

Hepatic injury can occur, with varying degrees of involvement, in patients who have sickle cell syndromes. In 1953, Green and associates¹ published the first major report concerning liver involvement in sickle cell anemia. They retrospectively analyzed 21 autopsied cases of sickle cell anemia as well as an additional 29 patients with ongoing disease. Hepatomegaly had been present at some time in most cases, especially during crises. Some patients had a marked increase in the total and direct bilirubin levels. The postmortem examinations revealed hepatomegaly and dilated hepatic sinusoids filled with erythrocytes, Kupffer's cell hypertrophy with red cell engulfment, and, in some cases, cirrhosis. Described as postnecrotic, the cirrhosis was found to be most severe centrally. Also noted were hemosiderin granules in both hepatocytes and Kupffer's cells, hepatocellular dropout, and dilated biliary canaliculi without obstructing lesions.

Since then, many authors have studied liver involvement in sickle cell disease. It is estimated² that hepatopathy occurs in 10 percent of sickle cell patients seeking medical treatment, and that hepatic involvement can occur with or without

painful crises. Diggs² stated that episodes of "hepatogenous jaundice" are recurrent in these cases, and that liver function worsens with age or pregnancy. Clinically, hepatomegaly is a recurrent theme. Ballas and coworkers³ postulated that because the serum albumin level was normal in these cases, the liver enlargement is secondary to increased reticuloendothelial activity rather than parenchymal disease. More severely ill patients can present with right-upper-quadrant pain, fever, and leukocytosis. In extreme cases, death can ensue.⁴⁻⁶ However, according to Buchanan and Glader,⁷ children with hyperbilirubinemia in sickle cell anemia usually have a benign course.

In this paper, we report a severe case of sickle cell hepatopathy (hepatic crisis) that was treated by partial exchange transfusion. The literature regarding the pathology, diagnosis, and treatment of liver damage associated with sickle cell disease also is reviewed.

Report of case

A 20-year-old black man was admitted to Kennedy Memorial Hospital-University Medical Center with a chief complaint of epigastric pain and scleral icterus of 1 week's duration. The patient described the pain as dull, without radiation, and he reported clay-colored stools and dark urine. He denied previous transfusion, drug abuse, or hepatitis. His past medical history was significant for sickle cell-thalassemia, multiple painful crises. He was on a regimen of folic acid and iron supplements.

Physical examination revealed the patient to be afebrile and in mild abdominal distress. Examination of the eyes showed scleral icterus. The neck was devoid of

adenopathy. The heart had a 3/6 systolic ejection murmur, and the lungs were normal. The abdomen was soft and nontender to palpation, with normal bowel sounds. The liver was percussed to 15 cm. in height at the mid-clavicular line; the gallbladder was not palpable. The stool specimen was acholic and hematest negative.

Admission laboratory studies revealed the following values: total and direct bilirubin, 35.8 mg./dl. and 18 mg./dl., respectively; alkaline phosphatase, 540 I.U.; serum glutamic-oxaloacetic transaminase (SGOT), 292 I.U.; serum glutamic-pyruvic transaminase (SGPT), 192 I.U.; lactic dehydrogenase, 279 I.U.; and cholesterol, 92 mg./dl. The serum amylase and lipase levels and prothrombin time were normal. The urine was positive for bilirubin. Hemoglobin electrophoresis showed 94 percent hemoglobin S and 6 percent hemoglobin A₂. The complete blood count revealed a hemoglobin concentration of 10.1 gm./dl. and a hematocrit reading of 29.9 percent. The erythrocyte count was 3.46 million/cu. mm., the platelet count was 384,000/cu. mm., and the differential count included 8.3 percent reticulocytes. The haptoglobin value was less than 30 mg./dl., and both the urine-free hemoglobin and urine hemosiderin tests were negative. Hepatitis A and B studies were negative.

Following admission, the patient's abdominal pain subsided. His iron supplements were discontinued. Biliary tract ultrasonography showed gallbladder sludge and normal ducts. The patient received three partial exchange transfusions over the next 3 days. Red cell mass was estimated to be 30 cc./kg. An appropriate number of units were transfused to exchange his volume one time to bring about a 50 percent reduction in hemoglobin S. At that time, his total bilirubin value had decreased to 13.1 mg./dl., with a direct component of 5.5 mg./dl. The SGOT and SGPT levels were 174 I.U. and 206 I.U., respectively. Repeat hemoglobin electrophoresis showed hemoglobin A at 45 percent, hemoglobin S at 45 percent, and hemoglobin A₂ at 10 percent.

The patient was discharged and scheduled for outpatient liver biopsy and endoscopic retrograde pancreatography, but he never returned for these procedures. A follow-up call to his family doctor revealed that his bilirubin levels were almost normal, and that he was asymptomatic.

Discussion

Pathologic findings

Histologically, little is to be added to Green and associates¹ original description. What appears to be specific for hepatic crisis are the presence of agglutinated and sickled red blood cells in dilated sinusoids and hypertrophied Kupffer's cells containing sickled erythrocytes. Other findings include platelet and fibrin deposition in the hepatic sinusoids, decreased hepatic glycogen, and mitochondrial and endoplasmic reticulum abnor-

malities. Iron deposition and both micro- and macro-nodular forms of cirrhosis have been described. Rosenblate and coworkers⁸ biopsied unselected sickle cell patients with and without abnormal liver function tests and found the histologic pattern to be similar in both groups. Shulman and Beem⁹ reported anaerobic liver abscess in a secondarily infected sickle cell infarct. Pathophysiologically, it is thought that the liver damage is due to anoxic changes, which are caused by blood flow impairment resulting from sinusoidal blockage by red cells and thrombi.^{5,8}

Diagnosis

Laboratory evidence of sickle hepatopathy typically will include elevated direct and total bilirubin values. In fact, a total bilirubin level >25 mg./dl. suggests a poor prognosis.² Transaminase elevations are common, but they generally do not exceed 300 I.U. except in severe cases of hepatopathy.^{4,6} Hilkwitz and Jacobsen¹⁰ reported abnormal liver function test results in both asymptomatic and symptomatic patients. The most commonly involved genotypes are SS, S-Thal, and SC.

One problem with many of the reported cases was the inability to exclude viral hepatitis or alcohol as the etiologic agent of liver damage. Johnson and coworkers¹¹ biopsied 9 sickle cell patients with persistent liver function abnormalities, and in each case found secondary liver problems complicating the sickle cell disease. These included chronic active hepatitis B, acute viral hepatitis, common duct obstruction, sarcoidosis, granulomatous hepatitis, and alcoholic liver disease. On the other hand, Bauer and associates¹² reported 7 sickle cell patients with micronodular cirrhosis for which no other etiology could be found.

The major diagnostic considerations in a jaundiced patient with sickle cell anemia and an elevated direct bilirubin level are choledocholithiasis, viral hepatitis, and sickle cell hepatopathy. In our case, types A and B viral hepatitis were excluded. The non-A/non-B type was unlikely because of the patient's lack of exposure to blood products or to an acute case of hepatitis. Because of normal findings on biliary ultrasonography, choledocholithiasis also was improbable. It was unfortunate that endoscopic retrograde pancreatography was not performed to rule out gallstones unequivocally, but, as noted, the patient refused to return for the procedure. Liver biopsy would have been useful in excluding viral hepatitis and in documenting the characteristic changes of sickle cell hepatopathy.

Treatment

Exchange transfusion has been utilized successfully in the treatment of hepatic crisis. The goal of such treatment should be to reduce hemoglobin S levels to less than 40-50 percent. This will reduce blood resistance and help to maintain a normal microcirculation.

Brody and coworkers¹³ treated 8 patients with painful crises with a 48-hour exchange totaling 1,000 cc. in and 1,000 cc. out. Clinical improvement was noted in these cases. Lanzkowsky and associates¹⁴ treated 17 children by exchange transfusion for either a complication of sickle cell disease or preoperatively. Three of the children had hepatic crises. The exchange consisted of transfusing 15 ml./kg. of packed red blood cells and removing 20 ml./kg. of whole blood. This was repeated 24 hours later, with the average total bilirubin value of 30 mg./dl. decreasing to 13 mg./dl. after the second transfusion. The patients' hemoglobin S concentrations also had been reduced, to less than 50 percent. Sheehy and associates¹⁵ treated 1 case of liver failure secondary to sickle hepatopathy by exchange transfusion with success.

In our case, three partial exchange transfusions over a 3-day period succeeded in lowering the total bilirubin value from 35.8 mg./dl. to 13.1 mg./dl. The hemoglobin S concentration was reduced from 94 percent to 45 percent.

In cases in which surgery is required, exchange transfusions may be beneficial preoperatively to allow for safe anesthesia and to prevent intraoperative crises.¹⁶⁻¹⁸

Exchange transfusion is not without risk, because viral hepatitis, AIDS infection, or a transfusion reaction can occur. Therefore, this treatment should be reserved for the more severe cases of hepatic dysfunction.

Summary

Sickle cell hepatopathy occurs with varying degrees of severity, ranging from asymptomatic histologic changes in the liver to death from fulminant hepatic failure. Children typically run a benign course. When the patient is jaundiced, one must exclude viral hepatitis and extrahepatic obstruction. Persistent abnormalities require a liver biopsy to rule out other causes of liver disease. Characteristic pathologic changes include agglutinated red blood cells and fibrin plugs obstructing the hepatic sinusoids, as well as Kupffer's cell erythrophagocytosis and hypertrophy. The liver

damage is caused by anoxic changes that are secondary to erythrocyte sludging. Exchange transfusion may be helpful in the more severe cases, particularly when the total bilirubin level exceeds 25 mg./dl. The goal of therapy is to reduce the hemoglobin S concentration to less than 40-50 percent.

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Contraindications: Anaphylactoid reactions have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Because of the possibility for cross-sensitivity, TOLECTIN should not be given to patients in whom aspirin and other nonsteroidal anti-inflammatory drugs (particularly zomepirac sodium) induce symptoms of asthma, rhinitis, urticaria or other symptoms of allergic or anaphylactoid reactions. Patients experiencing anaphylactoid reactions on TOLECTIN should be treated with conventional therapy, such as epinephrine, antihistamine and/or steroids.

Warnings: Give under close supervision to patients with a history of upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" section. Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. If TOLECTIN must be given to patients with active peptic ulcer, closely supervise for signs of ulcer perforations or severe gastrointestinal bleeding.

Precautions: Patients who develop visual disturbances during treatment with TOLECTIN should have ophthalmologic evaluations and follow-up.

Cases of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported. Closely monitor patients with impaired renal function; they may require lower doses.

In patients with pre-renal conditions leading to a reduction of renal blood flow or blood volume, administration of an NSAID may precipitate overt renal decompensation. Patients at greatest risk are those with heart failure, liver dysfunction, those taking diuretics, and the elderly.

TOLECTIN prolongs bleeding time. Patients who may be adversely affected by prolongation of bleeding time should be carefully observed when TOLECTIN is administered.

In patients receiving concomitant TOLECTIN-steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

TOLECTIN should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

A patient with symptoms and/or signs suggesting liver dysfunction,

or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with TOLECTIN. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with TOLECTIN as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), discontinue TOLECTIN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Tolmetin sodium did not possess any carcinogenic liability, mutagenic potential or impairment of fertility in standard *in vitro* tests and/or in tests in animals. Effects on parturition (including increased incidences of dystocia and delayed parturition) have been shown, however, as with other prostaglandin inhibitors.

Pregnancy:—TOLECTIN has not been studied in pregnant women. Drugs in this class have known effects on the fetal cardiovascular system which may cause constriction of the ductus arteriosus *in utero* during the third trimester of pregnancy, which may result in persistent pulmonary hypertension of the newborn. Therefore, TOLECTIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:—Because TOLECTIN is secreted in human milk, nursing should not be undertaken while a patient is on this drug.

Pediatric Use:—The safety and effectiveness of TOLECTIN for children under 2 years of age have not been established.

Drug Interactions:—Increased prothrombin time and bleeding have been reported in patients on concomitant TOLECTIN and warfarin therapy; caution should be exercised when administering TOLECTIN to patients on anticoagulants.

Drug/Laboratory Test Interaction:—Metabolites of tolmetin in urine have been found to give positive tests for proteinuria using tests which rely on acid precipitation as their endpoint. No interference is seen in the tests for proteinuria using dye-impregnated commercially available reagent strips.

Drug-Food Interaction:—In a controlled single dose study, administration of TOLECTIN with milk had no effect on peak plasma tolmetin concentration, but decreased total tolmetin bioavailability by 16%. When TOLECTIN was taken immediately after a meal, peak plasma tolmetin concentration and total bioavailability were reduced by 50% and 16%, respectively.

Adverse Reactions: Incidence Greater Than 1%:—The following adverse reactions which occurred more frequently than 1 in 100 were reported in controlled clinical trials.

Gastrointestinal: Nausea (11%), dyspepsia, "gastrointestinal distress," abdominal pain, "diarrhea," flatulence, "vomiting," constipation, gastritis, and peptic ulcer.

Body as a Whole: Headache, "asthenia," chest pain

Cardiovascular: Elevated blood pressure, "edema"

Central Nervous System: Dizziness, "drowsiness, depression

Metabolic/Nutritional: Weight gain, "weight loss"

Dermatologic: Skin irritation

Special Senses: Tinnitus, visual disturbance

Hematologic: Small and transient decreases in hemoglobin and hematocrit not associated with gastrointestinal bleeding have occurred.

Urogenital: Elevated BUN, urinary tract infection

*Reactions occurring in 3% to 9% of patients treated with TOLECTIN. Reactions occurring in fewer than 3% of the patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable):

Gastrointestinal: Gastrointestinal bleeding with or without evidence of peptic ulcer, glossitis, stomatitis, hepatitis, liver function abnormalities

Body as a Whole: Anaphylactoid reactions, fever, lymphadenopathy, serum sickness

Hematologic: Hemolytic anemia, thrombocytopenia, granulocytopenia, agranulocytosis

Cardiovascular: Congestive heart failure in patients with marginal cardiac function

Dermatologic: Urticaria, purpura, erythema multiforme, toxic epidermal necrolysis

Urogenital: Hematuria, proteinuria, dysuria, renal failure

Incidence Less Than 1% (Causal Relationship Unknown):

Body as a Whole: Epistaxis

Special Senses: Optic neuropathy, retinal and macular changes

Full directions for use should be read before administering or prescribing.

For information on symptoms and treatment of overdose, see full prescribing information.

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