

Liver Biopsy in Hemophilia A

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Hepatitis is a significant complication of the treatment of hemophilia A with factor VIII concentrates. Chronic liver disease in these patients is infrequently documented in the literature. The results of percutaneous liver biopsy, under the coverage of glycine-precipitated factor VIII, in six patients with hemophilia A who had the persistence of abnormal liver-function tests for at least 6 months, are described. Three patients had chronic active hepatitis, and three had chronic persistent hepatitis. No complications were encountered as a result of the biopsy procedure. These results suggest that percutaneous liver biopsy should be considered in patients with hemophilia A with continuously abnormal liver-function tests to establish a histologic diagnosis and to guide further therapy.

THE DEVELOPMENT OF FACTOR VIII concentrates (cryoprecipitated and glycine-precipitated factor VIII) from plasma has greatly simplified and facilitated the care of patients with hemophilia A. However, a major disadvantage of these products is that they carry the risk of exposing the patient to various hepatitis-causing viruses. There has been an increased number of cases of clinically apparent hepatitis since the introduction of these concentrates (1-3). The high prevalence of hepatitis B surface antigen (HBsAg) (4) and antibody to this antigen (anti-HBs) (5) is further proof of the increased exposure of these multitransfused patients to hepatitis B virus (HBV) whether or not there is a history of clinical hepatitis.

Liver function tests may remain abnormal for long periods of time in these multitransfused patients. In such cases, the differential between chronic active hepatitis and chronic persistent hepatitis is an important one in that the former may lead to cirrhosis and often requires corticosteroid therapy (6, 7). The differentiation between these two diagnoses usually requires percutaneous liver biopsy (8, 11). Administration of factor VIII concentrates sufficient to raise factor VIII concentrations to relatively normal levels has allowed patients with hemophilia A to undergo minor and major surgical procedures (12). However, there are no reports of percutaneous liver biopsies being done in hemophilic patients with hepatitis. This report deals with our experience with percutaneous liver biopsy in six patients with hemophilia A with chronically abnormal liver function tests.

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Patients and Methods

PATIENTS

Patients presenting to the Hemophilia Clinic of North Carolina Memorial Hospital are routinely screened for evidence of liver disease. When clinical and biochemical evaluation suggest viral hepatitis, each patient is followed for evidence of the development of chronic hepatitis. Since 1972, six patients have been followed who have had persistent elevation of serum transaminase values of greater than twice normal, often in association with other signs and symptoms of chronic hepatitis. Every effort was made to exclude drug-induced, alcohol-related, and inherited liver diseases. When abnormalities of this severity persisted for at least 6 months, percutaneous liver biopsy was done to establish a histologic diagnosis and to guide further therapy.

PREPARATION OF THE PATIENT

The patients were admitted to the hospital 24 h before the liver biopsy. Each patient was checked for the presence of an inhibitor of factor VIII using the inhibitor assay of Roberts and associates (13). If no inhibitor was present, the patient received an infusion of glycine-precipitated factor VIII calculated to raise his factor VIII level to 100%. Blood was drawn at 15 min, 1, 3, 6, 9, and 12 h after the infusion was completed. With each sample, a factor VIII assay was done to be certain that the in-vivo recovery and biologic half-life of factor VIII were normal. If an inhibitor was found, the biopsy was not done. If the fall-off study was normal, glycine-precipitated factor VIII, calculated to raise the factor VIII level to approximately 100%, was again administered during a short period of time just before the liver biopsy. Immediately after this infusion, the biopsy was done using the Klatzkin needle (14), and the patient was begun on a constant infusion of factor VIII (15) calculated to maintain the factor VIII level of the patient at about 75% of normal. The amount of infusate was adjusted according to factor VIII assay results and was continued for 72 h after the biopsy.

MATERIALS AND METHODS

The blood for the coagulation studies was collected in plastic syringes using one-part 3.2% citrate to eight parts blood. The partial thromboplastin time (PTT) using Thrombofax (Ortho Diagnostics; Raritan, New Jersey) was done by the method of Rodman, Barrow, and Graham (16). Factor VIII assays were done by the one-stage assay using known factor VIII-deficient substrate as described by Barrow, Bullock, and Graham (17). Inhibitors to factor VIII were searched for by the method of Roberts and associates (13) and by determining the plasma half-life of factor VIII. The HBsAg and anti-HBs were done by the solid-phase radioimmunoassay technique (Ausria II; Abbott Laboratories; North Chicago, Illinois).

PATHOLOGY

All of the liver biopsies were reviewed by one of the authors (HL) and by Dr. Joseph Grisham of the Department of Pathology. Chronic persistent hepatitis and chronic active hepatitis were defined histologically in accord with the description of Fallon (18). Cirrhosis was diagnosed only if there were areas where the normal lobular architecture was no

Table 1. Patient Characterization

Case	Age yrs	Factor VIII Level %	Past Therapy*	Signs and Symptoms Liver Disease	Diagnosis
1	36	6	GP	Acute hepatitis—yes Fatigue Hepatomegaly, spider angiomas	Chronic active hepatitis
2	42	<1	WB, P, cryo. GP	Acute hepatitis—no Abdominal pain Hepatosplenomegaly	Chronic active hepatitis and cirrhosis
3	51	3	WB, P, cryo.	Acute hepatitis—yes Fatigue, abdominal pain Jaundice, fever, hepatomegaly	Chronic active hepatitis
4	23	<1	WB, P, cryo. GP	Acute hepatitis—no No symptoms or signs	Chronic persistent hepatitis
5	26	30	Cryo., GP	Acute hepatitis—yes Malaise	Chronic persistent hepatitis
6	27	<1	WB, P, cryo. GP	No physical signs Acute hepatitis—no Intermittent fatigue No physical signs	Chronic persistent hepatitis

* WB = whole blood; P = plasma; Cryo = cryoprecipitate; GP = glycine-precipitated factor VIII concentrates.

longer apparent and regenerating nodules and fibrosis had formed.

Results

No complications occurred from the liver-biopsy procedure. Of the six patients biopsied, two had chronic active hepatitis, one had chronic active hepatitis and early cirrhosis, and three had chronic persistent hepatitis.

Table 1 summarizes the historical and clinical aspects of the six patients. (See Appendix for details of each case.) Each patient had received various types of blood products during his life, but only three had clinically documented acute viral hepatitis. Five of the six patients had intermittent clinical symptoms of chronic liver disease during the months before biopsy. Physical findings of chronic liver disease were limited to the three patients who eventually had chronic active hepatitis on biopsy. All three had hepatomegaly and one presented with prolonged jaundice (Case 3).

Table 2 summarizes the duration of abnormal liver function tests and the values of these tests at the time of biopsy. All patients had abnormal tests for longer than 6 months, with three having abnormalities for longer than 12 months. HBsAg was detected in two of three patients with chronic active hepatitis and in none with chronic persistent hepatitis. All six patients were anti-HBs-positive. The three who eventually showed chronic active hepatitis on biopsy differed from those with chronic persistent hepatitis in that each had elevated bilirubin and total globulins.

The three patients showing chronic persistent hepatitis were not given corticosteroids. During a 2-year follow-up period, none has shown clinical or biochemical evidence of progression of his disease although all have continued to have elevated serum transaminase values. The three patients with chronic active hepatitis were given prednisolone in tapering doses. Two patients responded favorably with clinical and biochemical remission and are presently off all medications with no evidence of relapse. The third patient (Case 1) remains on corticosteroid therapy and has clinical

signs of progression to cirrhosis (that is, ascites, edema, and esophageal varices on barium study). There have been no significant side-effects from corticosteroid therapy in any patient.

Discussion

The development of factor VIII concentrates has allowed easier and more effective treatment of hemophilia A. One of the adverse side-effects has been the development of viral hepatitis. Screening each donor for HBsAg has decreased, but not eliminated, the exposure to HBV (19) and does nothing to decrease hepatitis caused by other viruses (20, 21). Most attention has been focused on clinically apparent episodes of hepatitis. We know, however, that anicteric, clinically inapparent hepatitis must be frequent because of the increased incidence of HBsAg (6%) and anti-HBs (73%) found in 109 patients with hemophilia followed at our institution during a 2-year period. Only 25% of this group had a clinical history of hepatitis (22).

Chronic liver disease after post-transfusion hepatitis continues to be a significant problem in patients without hemophilia (23). Chronic liver disease in patients with hemophilia A is infrequently documented in the literature (3). A recent retrospective autopsy evaluation of the cause of death in patients with hemophilia showed no occurrence of cirrhosis and a 3% to 5% frequency of hepatitis (24). Review of six patients with hemophilia A who came to autopsy at our institution (1959 through 1973) showed that all died from hemorrhagic complications and none had evidence of liver disease. Mannucci and colleagues (4) found a high frequency of abnormal liver-function tests in their 91 asymptomatic patients with severe hemophilia, of whom 18% gave a history of jaundice. Serum transaminase values were elevated in 45%; gamma-globulin in 34%; gamma glutamyltranspeptidase in 27%; alkaline phosphatase in 23%; and bilirubin in 13%. Serum albumin was depressed in 13%. The 70% with either a positive HBsAg or anti-HBs had a higher incidence of abnormal liver-

function tests than the 30% without HBsAg or anti-HBs. However, the duration of these abnormal liver-function tests was not mentioned, and liver biopsies were not done to identify the liver histology. It is our fear that liver disease may become a significant cause of morbidity and mortality in these patients as hemorrhagic complications are reduced with improved concentrate therapy.

This report shows that patients with hemophilia A may develop significant chronic liver disease. The patients reported here had the persistent abnormalities of liver function for at least 6 months. We felt that this was an indication to consider liver biopsy to define the severity of the liver disease and to consider the need for further therapy (that is, corticosteroids).

Chronic active hepatitis cannot be reliably differentiated from chronic persistent hepatitis in the early stages of the disease by clinical and biochemical variables alone (8-11). This small group of patients underscores the need for liver biopsy to differentiate chronic active hepatitis from chronic persistent hepatitis. Symptoms of liver disease were present in all three of our patients with chronic active hepatitis but were also present in two of the three with chronic persistent hepatitis. Three physical and biochemical abnormalities were found only in patients with chronic active hepatitis: hepatomegaly, increased total bilirubin, and increased total globulins. These three findings may be signs of disease that has become more extensive. As patients without bleeding disorders and persistent liver-function abnormalities are being biopsied earlier in the course of their liver disease, it is now recognized that the pathologic changes of chronic active hepatitis can be seen on biopsy before many of these clinical and biochemical abnormalities develop (6, 10, 23, 25, 26). If it is true that the morbidity and mortality from

the disease is greatly reduced by treatment with corticosteroids in the early stages (8), liver biopsy should not be postponed until more advanced signs of the disease are present.

The question becomes whether the risk of liver biopsy in patients with hemophilia A with chronic active hepatitis is greater than the advantages to be gained from corticosteroid therapy. During the past decade, various controlled trials on the use of corticosteroids in treatment of chronic active hepatitis with and without cirrhosis have appeared (6, 7, 27, 28). The results of these trials strongly suggest that corticosteroids should be instituted if chronic active hepatitis is found. Some investigators have questioned their use in various subpopulations of patients with chronic active hepatitis (especially asymptomatic individuals and those with the persistence of the HBsAg) (29). Controlled trials in these various subpopulations are being formulated (30). Until further information is acquired, it appears that corticosteroid therapy should be considered in patients with biopsy-proven chronic active hepatitis. On the other hand, there is no proven efficacy of corticosteroids in the therapy of chronic persistent hepatitis (9). The adverse side-effects of corticosteroids are well documented (30), and these may be magnified in patients with hemophilia, making therapy with these medications dangerous without histologic documentation of the liver disease.

At the present time, when we consider all these factors and combine them with our lack of morbidity from liver biopsy, we conclude that the potential risks of complications from liver biopsy in hemophilia A patients are outweighed by the therapeutically important histologic information gained from the biopsy. It is our hope that in the years to come, clinical and biochemical variables will

Table 2. Values of Liver-Function Tests at the Time of Liver Biopsy

Case	Diagnosis	Duration of Abnormal Liver-Function Tests	Total Bilirubin*	Alkaline Phosphatase†	SGOT‡	SGPT‡	Albumin§	Total Globulins§	HBsAg	Anti-HBs
<i>months</i>										
Normal values	0 to 1.2	2 to 6	8 to 40	8 to 35	3.5 to 5.0	1.7 to 3.3
1	Chronic active hepatitis	8	1.7	8.5	269	189	4.5	4.2	+	+
2	Chronic active hepatitis	8	1.4	3.4	183	194	4.3	3.4	-	+
3	Chronic active hepatitis	24	8.7	22.8	518	263	3.6	3.4	+	+
4	Chronic persistent hepatitis	7	0.6	8.1	158	258	3.8	3.2	-	+
5	Chronic persistent hepatitis	24	0.7	3.4	84	183	4.8	3.1	-	+
6	Chronic persistent hepatitis	12	0.3	2.9	170	131	4.8	2.9	-	+

* Units of mg/dl.

† Nitrophenol units.

‡ Sigma-Frankel units; SGOT = serum glutamic oxalacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

§ Units of g/dl.

|| HBsAg = Hepatitis B surface antigen; anti-HBs = antibody to HBsAg.

allow the important differentiation between chronic active hepatitis and chronic persistent hepatitis without the need for histologic documentation. Until that time, we feel that percutaneous liver biopsy, using the methods that we have adopted, should be considered in patients with hemophilia A, chronically abnormal liver-function tests, and signs and symptoms of chronic liver disease.

Hepatitis is also common in hemophilia B (1, 3, 4) and other hemophiloid disorders. Presently, however, we would not favor liver biopsies in those patients requiring coverage with prothrombin complex concentrates because of the known complications of these products in patients with liver disease (32-34).

Appendix

CASE HISTORIES

Case 1: This patient is a 36-year-old man with mild hemophilia A (factor VIII, 6%). Six to 8 weeks after his first infusion of glycine-precipitated factor VIII concentrate in June 1972, he developed symptomatic, HBsAg-positive hepatitis. Liver-function test values remained abnormal for longer than 6 months, serum transaminase values at times being more than 1000 U. Eight months after the onset of jaundice, he was admitted for liver biopsy. Positive physical findings were limited to multiple spider angiomas and an enlarged liver of 14 cm. At the time of biopsy, several liver-function tests were abnormal (see Table 2). The biopsy was done without complication on 4 April 1973, after the procedure noted above. The interpretation of the biopsy was chronic active hepatitis, and the patient was begun on prednisolone therapy. He has remained on these medications for 4 years with no side-effects, but he has developed clinical signs of cirrhosis (that is, fluid retention and esophageal varices on barium study).

Case 2: This patient is a 42-year-old man with severe hemophilia A (factor VIII, 1%). He has received multiple transfusions of whole blood, plasma, cryoprecipitate, and glycine-precipitated factor VIII concentrates. In May 1973, he was first noted to have elevated serum transaminase values at a time when he was on home therapy with cryoprecipitate. In December 1973, he was evaluated for several episodes of abdominal pain and a nonvisualizing oral cholecystogram. Liver-function tests at that time showed a serum glutamic oxalacetic transaminase (SGOT) of 110 U, bilirubin of 1.4 mg/dl, and an alkaline phosphatase of 3.9 U. With observation the transaminase values improved. However, when he was admitted for elective cholecystectomy 1 month later, his liver-function test results were more abnormal (see Table 2). Clinical evidence of liver disease included an enlarged liver and a palpable spleen. On 17 January 1974, a percutaneous liver biopsy was done without complication. It showed chronic active hepatitis and cirrhosis. Thus, the cholecystectomy was postponed, and he was begun on prednisolone therapy. These medications were withdrawn after 1 year with clinical and biochemical resolution of his disease, and he has shown no evidence of relapse.

Case 3: This patient is a 51-year-old man with moderate hemophilia A (factor VIII, 3%). During his life, he has received numerous transfusions of whole blood, plasma, and cryoprecipitate without difficulty. In October 1972, he underwent herniorrhaphy under cover of cryoprecipitate. Three months later, he developed symptoms and biochemical abnormalities consistent with hepatitis. During the next 2 years, he had persistent fatigue, malaise, and episodes of nausea, vomiting, jaundice, and abdominal pain. Bilirubin, alkaline phosphatase, and transaminase values had been chronically elevated, and an oral cholecystogram had not visualized (at a time when his bilirubin was normal). Because of an episode of abdominal pain, he was referred to our hospital where he was found to have jaundice, fever, and hepatomegaly with a liver span of 13 cm. There were no other clinical signs of chronic

liver disease. Initial laboratory values were: SGOT, 1200 U; serum glutamic pyruvic transaminase (SGPT), 463 U; alkaline phosphatase, 43 U; and total bilirubin, 8 mg/dl. After 2 days, the pain and fever subsided and liver-function tests showed improvement (see Table 2). Percutaneous liver biopsy was done without complication on 21 February 1975. It showed chronic active hepatitis, and he was begun on prednisolone therapy. These medications were withdrawn after 1 year with clinical and biochemical resolution of his disease, and he has shown no evidence of relapse.

Case 4: This patient is a 23-year-old man with severe hemophilia A (factor VIII, < 1%). Bleeding episodes had been controlled by the use of whole blood, plasma, and cryoprecipitate until 1970 when glycine-precipitated factor VIII concentrates were first used. During an evaluation for knee surgery in September 1973, he was first noted to have abnormal liver-function tests. At no time did he have clinical symptoms suggestive of hepatitis. Because of the liver-function abnormalities (and an upper gastrointestinal bleed in October 1973), surgery was postponed until February 1974, when he had insertion of a Welldium endoprosthesis to replace his right knee in spite of mildly elevated serum transaminase values. During his recovery, liver-function test results were abnormal (see Table 2). Liver biopsy was done without complication on 26 April 1974. Interpretation of the biopsy was chronic persistent hepatitis. No further therapy was given, and he continues to have mild elevation of his serum transaminase levels without clinical signs of progression of his liver disease.

Case 5: This patient is a 26-year-old man with mild hemophilia A (factor VIII, 30%). He experienced only mild bleeding after a dental extraction and after a tonsillectomy. At age 21, he had a traumatic hemarthrosis and hemophilia was diagnosed for the first time. In 1972, he had an elective laminectomy for herniated nucleus pulposus, and postoperatively received his first replacement therapy with cryoprecipitate and glycine-precipitated factor VIII concentrates. Several weeks later, he developed symptoms of hepatitis and serum transaminase levels of greater than 1000 U. During the next 2 years, he had several episodes of malaise at which time serum transaminase values were greater than 500 U. Even when he was asymptomatic, SGOT levels were approximately 100 U. He had no evidence of liver disease on physical examination. When he was admitted for liver biopsy, the only liver-function test abnormalities were elevated serum transaminase values (see Table 2). The percutaneous liver biopsy was done without complication on 8 May 1974, and showed chronic persistent hepatitis. No further therapy was given, and he continues to have mild elevation of his serum transaminase levels without clinical signs of progression of his liver disease.

Case 6: This patient is a 27-year-old man with severe hemophilia A defected at birth (factor VIII, < 1%). His early bleeding problems were treated with whole blood, plasma, and cryoprecipitate. He first received glycine-precipitated factor VIII concentrates in 1972 and began home treatment with this product. In November 1974, he was first noted on routine screening to have elevated serum transaminase levels. The SGOT remained between 100 to 300 U on all measurements for the next 12 months, and he had intermittent fatigue and malaise. Physical examination showed no stigmata of liver disease. Before liver biopsy on 10 November 1975, the only liver-function test abnormalities were elevated serum transaminase values (see Table 2). The percutaneous liver biopsy was without complications and showed chronic persistent hepatitis. No further therapy was given, and he continues to have mild elevation of his serum transaminase levels without clinical signs of progression of his liver disease.

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