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Predictive Markers of Chronic Liver Disease in Hemophilia

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In an attempt to predict progressive liver damage in hemophiliac patients by noninvasive means, we conducted a retrospective analysis of clinical and laboratory data from 44 liver biopsies taken from 35 hemophiliac patients. This showed that serum IgG was normal in patients with chronic persistent hepatitis (CPH) but significantly elevated in those with chronic active hepatitis (CAH) or cirrhosis (CIR) ($P < .001$). Relationships were less significant between liver histology and IgM ($P < .01$), IgA ($P < .05$), and globulin ($P < .05$). This was unaffected by human immunodeficiency virus (HIV) antibody status in asymptomatic individuals. Although patients with progressive liver disease were also older than those with CPH ($P < .001$), the immunoglobulin abnormalities were independent of this. Neither clinical examination nor liver biochemistry at the time of biopsy were of significant diagnostic value. Our results indicate that in the absence of AIDS an elevated IgG level is a reliable indicator of progressive hemophilic liver disease. © 1987 by Grune & Stratton, Inc.

RECENT LIVER biopsy data show that progressive liver disease is a serious problem in hemophilia¹⁻³ and may be the most common cause of death among hemophiliac patients.⁴ Whereas most hemophiliac patients have minor degrees of liver disease such as chronic persistent hepatitis (CPH), a substantial proportion have chronic active hepatitis (CAH) or cirrhosis (CIR), usually without symptoms. Because these patients are at risk of developing clinical problems, early identification is important so that they may be followed and treated appropriately. Currently, liver biopsy is regarded as the only reliable method for distinguishing between nonprogressive hepatitis and more serious liver disease. Many clinicians are reluctant to resort to liver biopsy because of the inherent risks of the procedure; indeed, liver biopsy in hemophiliac patients has been suggested to be particularly hazardous.² Therefore, a simple and more readily available marker of severe hemophilic liver disease is needed. This prompted us to perform a retrospective analysis of clinical and laboratory data from our 35 biopsied hemophiliac patients to see whether any of these enabled us to distinguish patients with progressive liver disease from those with nonprogressive liver disease.

MATERIALS AND METHODS

Patients. Thirty-five patients underwent liver biopsy between 1977 and 1986. The selection criteria have been published elsewhere.¹ The mean age was 33.4 ± 18.2 years (Mean \pm 1 SD) (3 to 70 years) at the time of their first biopsy. Thirty-two had hemophilia A, 2 had hemophilia B, and 1 had von Willebrand's disease. Twenty-four were severely affected (factor VIII or IX $<2\%$), and 11 were mildly affected (factor VIII or IX $>2\%$). Nine of these had a second liver biopsy after a mean interval of 46.7 ± 21 months (range 24 to 96 months). Factor VIII or IX consumption during the 3 years prior to each biopsy was calculated from the hospital records and cross-checked with the patient's factor VIII or IX returns.

Liver biopsies. All liver samples were obtained using a Klatzkin needle with precautions as previously described.⁵ Details of the histological processing have also been described before.¹ The presence of microvesicular steatosis, sinusoidal infiltration, and periductal infiltration was construed as evidence of non-A, non-B hepatitis virus infection (NANB).^{6,7} All liver biopsies were stained, using an immunofluorescent method, for δ antigen.

Physical signs. All patients were seen every 6 months for blood sampling and physical examination. Over the past 4 years, this has been performed by the same physician each time.

Biochemistry. Serum aminotransferases, bilirubin, albumin, and globulin levels were measured using standard auto analyzer techniques. Prothrombin times were also measured at the time of biopsy, partly as a measure of hepatic function. All values outside

the reference range were considered abnormal. When three or more consecutive aminotransferase levels from a patient, covering a period of at least 1 year, were all normal, the patient's aminotransferase pattern was considered normal. When three or more tests covering a 2-year period were all abnormal and there was no evidence of a return to normal, the patient's aminotransferase pattern was considered persistently abnormal. Patients with at least three observations over a 2-year period not conforming to either pattern were considered to have an intermittently abnormal aminotransferase pattern.

Serology. Serum immunoglobulin levels were determined using an immunonephelometric assay using endpoint kinetics on a rapid centrifugal auto-analyzer (Baker Instruments, Encore). Antinuclear, anti-smooth muscle, and antimitochondrial antibodies were measured by indirect immunofluorescence, screened at a titer of 1 in 20; anti-dsDNA was measured by reverse passive hemagglutination.

Hepatitis B serology including HBsAg, anti-HBc, and anti-HBs were determined by radioimmunoassay (RIA) at the time of biopsy. IgM anti-HBc was also determined, using RIA, in patients who had no evidence of anti-HBs following a documented episode of hepatitis B, to exclude continuing active hepatitis B infection.

Human immunodeficiency virus (HIV) antibody was measured by RIA in stored serum samples taken serially between 1977 and 1986. The relationship between serum IgG level and HIV seroconversion and between serum IgG level was analyzed in 23 HIV antibody-positive hemophiliac patients, 15 of whom had undergone liver biopsy.

Statistics. Dividing the patients into those with CPH, those with CAH, and those with CIR, we analyzed the relationship between histological diagnosis and various parameters of possible predictive value. The relationship between liver histology and age, factor VIII or IX consumption in the 3 years prior to biopsy, and mean serum immunoglobulin and globulin levels during the year of biopsy was examined by analysis of variance. The relationship between liver histology and the degree of abnormality of the aminotransferases during the year of biopsy was analyzed using one-way nonparametric Kruskal-Wallis analysis of variance. Discriminant analysis was

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Table 1. Results of Serial Liver Biopsies

Patient	1	2	3	4	5	6	7	8	9	10	11	12
First biopsy	CPH	CPH	CPH	CPH	CPH	CPH	CPH	CPH	CAH	CAH	CAH	CAH
Second biopsy	CPH	CPH	CAH	CAH	CIR	CIR	CIR*	CIR*	CIR*	CPH	CIR	CIR

Abbreviations: CPH, chronic persistent hepatitis; CAH, chronic active hepatitis; CIR, cirrhosis.

*Not rebiopsied; clinical evidence of CIR including esophageal varices.

applied to combinations of mean IgG, IgM, and IgA levels during the year of biopsy in an attempt to improve the predictive power of IgG alone.

Because there was a significant positive correlation between progressive liver disease and both increased serum IgG and increasing age, it was important to establish whether serum IgG varied independently of age. Therefore, since CPH is not in itself associated with a raised IgG level,⁸ the relationship between IgG and age was analyzed in 24 hemophiliac patients, aged 3 to 66 years with biopsy-proven CPH. Using Kendall's rank correlation coefficient, all 137 IgG estimations from these patients were analyzed in relation to age at the time of sampling. The relationship between serum IgG level during the year of biopsy and the factor VIII consumption during the 3 years prior to biopsy was analyzed using Pearson's product-moment correlation coefficient for the 39 biopsies for which this information was available. The change in serum IgG level at the time of HIV antibody seroconversion was analyzed using Student's paired *t* test.

RESULTS

Initial biopsy in 35 patients showed CPH in 21, CAH in 9, and CIR in 5. Nine patients underwent a second biopsy, results of which are shown in Table 1. A further three patients developed esophageal varices and other physical signs of CIR (Table 1). Therefore, of the 44 liver samples from 35 patients, 24 had CPH, 11 had CAH, and 9 had CIR, and there is now clinical evidence of CIR in 3 other patients.

Histological stigmata suggestive of NANB hepatitis were found in 33 biopsies from 27 patients (20 CPH, 7 CAH, 6 cirrhosis). None of the liver samples had ground-glass or orcein-staining hepatocytes indicative of continuing intrahepatic HBV infection. HBsAg was not detected in the serum of any patient at the time of biopsy. Continuing HBV infection was suggested in one patient with CPH, who was biopsied 6 months after an episode of typical hepatitis B, by the presence of IgM anti-HBc.

Physical signs. Four patients, all with cirrhosis, had spider naevi. Eight patients had hepatomegaly (2 had CAH and 6 had CIR) at the time of biopsy. The spleen was palpable in 6 (in 3 with CPH, in 3 with CIR).

During a mean period of observation of 48 ± 26 months after biopsy, the spleen became palpable in 9 other patients (3 with CPH, 3 with CIR and 3 with clinical CIR). Thus, at the time of writing, 15 patients have a palpable spleen; 8 of these are now HIV antibody-positive (3 with CPH, 5 with CIR). Esophageal varices were demonstrable in only 3 of the 8 HIV-positive patients. Although 9 of our 12 patients with CIR have splenomegaly, esophageal varices were demonstrable in only 6. Three patients with CIR developed ascites and hepatic encephalopathy. All three died, two of hepatic failure and the third of intracranial haemorrhage. The number of

patients with abnormal physical signs was too small for statistical analysis.

Age at time of biopsy. Age at the time of biopsy (44 biopsies) differed significantly among the three groups of patients with CPH, CAH, and CIR; their mean ages were 28.2, 33.7, and 53.4 years, respectively ($P < .001$). The age of those with CIR was also significantly higher than those with CAH and those with CPH ($P < .05$).

Liver biochemistry. We could demonstrate no statistically significant relationship between the mean degree of elevation of the AST or ALT during the year of biopsy and the liver histology (Table 2). Serum bilirubin, serum albumin, and prothrombin time were invariably normal during the year of biopsy, but became abnormal during the last few months of life in the three patients who died. Mean serum globulin level was significantly higher in those with CIR ($P < .05$) than in those with CPH or CAH.

Serum immunoglobulins. Simultaneous immunoglobulin data were available for 41 of the 44 biopsies. There was a highly significant difference in mean IgG level during the year of biopsy among the three histological groups ($P < .001$), using the analysis of variance (Fig 1). The mean IgG level in the group with CIR was significantly higher than in both the CAH and the CPH group ($P < .05$). Similarly, the IgG level in the CAH group was significantly higher than in the group with CPH ($P < .05$). Patients with CPH had serum IgG levels consistently within the normal range, whereas IgG level did not reliably discriminate between CAH and CIR; the higher the serum IgG level, the more likely the presence of CIR. Discriminant analysis of combinations of IgG, IgM and IgA results failed to improve on the predictive value of IgG alone. Among the nine patients who underwent a second liver biopsy, progressive liver disease in six patients was associated with a rise in the mean IgG during the year of biopsy from 13.8 ± 2.4 g/L at the time of the first biopsy to 21.1 ± 8 g/L at the time of the second biopsy. Similar changes were observed in two patients with clinical evidence of progression to CIR in whom serial immunoglobulin levels were available. In contrast, in the three patients in whom the liver disease remained static or improved, IgG levels remained unchanged and within the normal range (Fig 2), but the number of observations was too small for statistical analysis.

Table 2. Mean AST and ALT in U/L During the Year of Biopsy in Relation to Biopsy Result

	CPH (n = 25)	CAH (n = 10)	Cirrhosis (n = 9)
AST (7-40 U/L)	72 \pm 48	143.2 \pm 126	89.1 \pm 40.8
Range	23-137	52-448	33-167
ALT (7-45 U/L)	131.6 \pm 95.4	197 \pm 109	116 \pm 94
Range	22-407	77-420	53-372

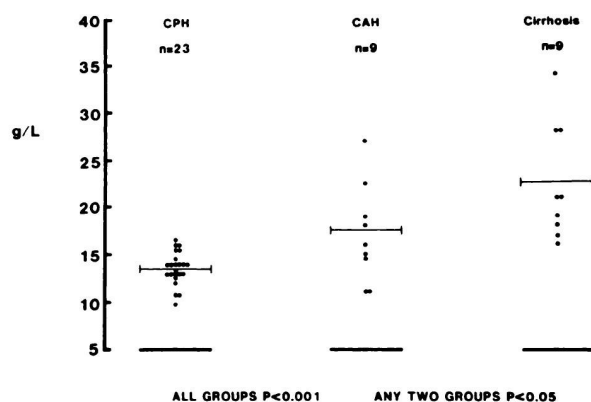


Fig 1. Relationship between IgG and liver histology for 41 liver biopsies; normal range 5.3 to 16.5 g/L.

No relationship between factor VIII use in the 3 years prior to biopsy and serum IgG level could be demonstrated for the 39 biopsied patients for whom this information was available ($r = -.1408$, $P = .20$). Similarly, no significant relationship could be demonstrated between serum IgG level and age, using 137 observations from 24 patients with CPH ($r = .270$, $P = .448$).

Serum IgM levels varied significantly among the three groups ($P < .01$), using the analysis of variance. The mean IgM in the group with CIR was significantly higher than that in the group with CPH ($P < .05$) but not higher than that in the group with CAH, indicating limited predictive

power. Although IgA levels varied significantly between the three groups ($P < .05$), and was highest in those with CIR, no significant difference between any two groups could be demonstrated.

At the time of biopsy, only four of our patients were HIV antibody positive, and all had CPH and normal IgG levels. To determine the extent to which HIV virus infection might mask the relationship between IgG and liver disease, we studied 23 asymptomatic HIV antibody-positive hemophilic patients, including 16 with persistently abnormal, 6 with intermittently abnormal, and 1 with normal aminotransferase levels. There was no significant difference between the mean IgG in the year before HIV seroconversion as compared with the year following HIV seroconversion of 16.34 ± 3.4 g/L v 15.9 ± 3.4 g/L.

Autoantibodies. Autoantibodies were repeatedly absent from all patients.

Factor VIII treatment. No significant relationship appeared to exist between the factor VIII consumption in U/kg per year during the 3 years prior to biopsy and the histological diagnosis ($P > .05$). Although the group with cirrhosis had the lowest factor VIII consumption, presumably because 5 of the 10 were mildly affected by hemophilia, this difference did not achieve statistical significance.

DISCUSSION

Despite our extensive experience of liver biopsy in hemophilic patients without major complications, we were nevertheless concerned by the inherent risks of the procedure. This prompted us to analyze retrospectively the clinical and laboratory data from our 35 biopsied haemophilic patients to see whether any of these were associated with progressive liver disease.

The presence of abnormal physical signs was of diagnostic value in only a few patients. Although patients with spider nevi always had CIR, these were found in only 4 of the 12 patients with this complication. Splenomegaly correlated poorly with portal hypertension, since esophageal varices were demonstrated in only six of the nine patients with CIR and splenomegaly. Indeed, the discovery of a palpable spleen in the absence of esophageal varices in five HIV antibody-positive patients suggests that splenomegaly may be a feature of HIV infection, as suggested by Ludlam and colleagues.⁹ Splenomegaly was reported in hemophilic patients even before the advent of the HIV infection, however.¹⁰

We confirmed earlier observations that the degree of elevation of the aminotransferases is of no diagnostic value.^{3,11} Marginal elevations are found in all groups, and resolution of the biochemical abnormalities is observed in some subjects with developing CIR. The emergence of an intermittently abnormal pattern of aminotransferases in eight patients with CPH is consistent with the suggestion that CPH may be associated with this pattern of liver enzyme abnormality.^{8,12}

The incidence of progressive liver disease increased significantly with advancing age. This may reflect the greater time that older patients have had for their liver disease to develop. Alternatively, it may suggest a change in host response to

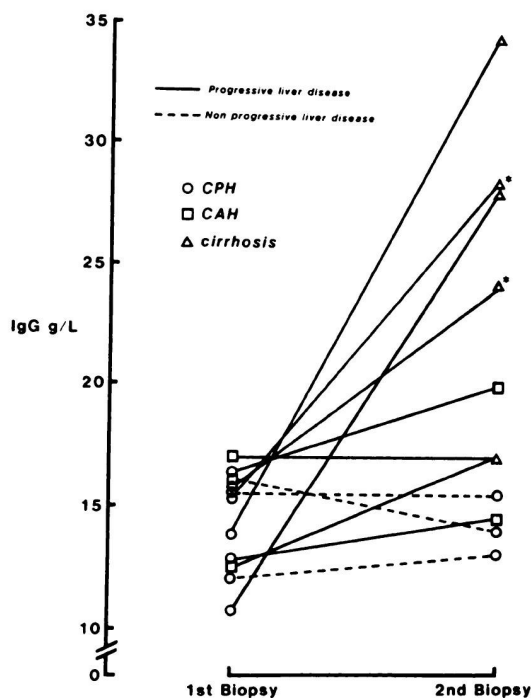


Fig 2. Change in IgG with both progressive and nonprogressive liver disease. *Clinical, not histological, evidence of cirrhosis and therefore not included in the analysis.

hepatotropic viruses with increasing age. It is unlikely to be accounted for by an increased total lifetime exposure to clotting factor concentrates, because we could find no relationship between the severity of the liver disease and the factor VIII consumption and because almost all patients develop NANB hepatitis after their first exposure to non-heat-treated factor VIII concentrate.¹³

Although it has been suggested that chronic HBV or δ infections are responsible for most cases of progressive hemophilic liver disease,^{14,15} we can demonstrate no such clear-cut relationship. Serological evidence of continuing HBV infection was found in only one biopsied patient, who had CPH. This is representative of our population, since only 4 of our 150 hemophilic patients are chronic HBV carriers. Similarly, δ infection was demonstrated in only six biopsied patients, all of whom have CPH. In contrast, 27 of the 35 biopsied patients have histological stigmata suggestive of NANB hepatitis. Therefore, having excluded other causes for liver disease, such as alcohol, HBV, and autoimmune disease, we believe that our biopsy group is etiologically a remarkably homogeneous one, in which most of the liver disease can be attributed to NANB hepatitis and very little to HBV or δ .

Hypergammaglobulinemia has been associated with CIR and CAH for many years,¹⁶ although we are unaware of any reports of it in chronic NANB hepatitis. Although serum globulin, IgM, and IgA levels were significantly increased in patients with progressive hemophilic liver disease, they did not discriminate reliably between the various histologic groups. In contrast, the serum IgG level appeared to be a reliable indicator of both progressive and nonprogressive hemophilic liver disease. The serum IgG levels in patients with CPH were tightly grouped within the normal range, confirming the observations of Chadwick and colleagues in CPH following hepatitis B.⁸ Although serum IgG did not reliably discriminate between CAH and CIR, serum IgG was significantly more elevated in patients with CIR than in those with CAH, and as the serum IgG level became higher, cirrhosis became progressively more likely. Progression of liver disease was almost invariably associated with a substan-

tial increase in serum IgG. In contrast, serum IgG remained unchanged in three patients in whom no change occurred between biopsies (Fig 2). There is no relationship between age and IgG in our hemophilic patients or indeed in normal subjects.¹⁷ All patients in our series with serum IgG levels >17 g/L had CAH or CIR. Twenty-five of 106 hemophilic patients seen in 1986 have IgG levels in this range, suggesting that the prevalence of CAH and CIR among hemophilic patients treated with blood products is ~25%. This is in close agreement with the report of a retrospective study of 155 unselected liver biopsy and necropsy specimens by Aledort and colleagues.² CPH was observed to progress to CAH or cirrhosis in six of our patients and is clearly less benign than had earlier been supposed.¹ In view of this, serum IgG should be measured at intervals in such patients to enable one to identify those developing progressive liver disease.

Although 50% of cases of AIDS-related complex (ARC)¹⁸ and most cases of AIDS¹⁹ have elevated IgG and IgA levels, our results are unaffected by this since none of our patients suffered with either disorder at the time of biopsy. Moreover, only four individuals, all with CPH and normal IgG levels, were HIV antibody positive at the time of biopsy. HIV antibody seroconversion per se was also unassociated with any change in IgG level, consistent with reports of normal immunoglobulin levels in most asymptomatic HIV antibody positive patients from other risk groups.¹⁸⁻²⁰ We therefore feel confident that in the absence of AIDS, ARC, or autoimmune disease an elevated serum IgG level is a reliable marker of severe hemophilic liver disease. This requires prospective confirmation by others.

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