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Health of the Intensively Treated Hemophiliac, With Special Reference to Abnormal Liver Chemistries and Splenomegaly

By Peter H. Levine, Bernard A. McVerry, Brian Attock, and Katharine M. Dormandy

Liver function abnormalities have been noted in intensively treated hemophiliacs, and have led to less aggressive application of pooled plasma products by some physicians. In a prospective study, liver function was abnormal in 68 of 98 hemophiliacs. The abnormalities of hepatic function tended to persist over a 1-yr study period. There was no correlation between these abnormalities and the age of the patient, the presence of hepatitis-associated antigen or antibody, the presence or absence of splenomegaly (which was found in 26 of 98 patients), the number of infusions of plasma products, the type of hemophilia, or the type of product infused. Titers of antibodies to cytomegalovirus were generally higher in hemophilic patients than in a control group of healthy volunteers. These abnormalities did not suggest that a less aggressive infusion regimen was indicated for the hemophiliac, but did suggest the need for careful long-term observation of such patients.

MANAGEMENT OF HEMOPHILIA has changed dramatically in recent years with the advent of concentrated plasma fractions and the development of the self-therapy method of treatment. Before such management was introduced, bleeding was often recognized and treated only after irreversible damage, particularly to joints, had occurred. Self-therapy has encouraged the patient to treat himself early and aggressively. It has reduced costs, decreased morbidity, normalized the life pattern, and slowed the progression of hemophilic arthropathy.[1]

The general health of the treated hemophiliac has seldom been subjected to systematic study since the attention of clinicians and investigators has pre-

From the Hemophilia Center, the Memorial Hospital, and the Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts; the Blood Coagulation Laboratory, Hematology Service, New England Medical Center Hospital and the Department of Medicine, Tufts University School of Medicine, Boston, Mass.; and the Haemophilia Center, Royal Free Hospital, London, England. The Memorial Hospital and the Royal Free Hospital are both International Hemophilia Training Centers of the World Federation of Hemophilia.

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Address for reprint requests: Dr. Peter H. Levine, The Memorial Hospital, 119 Belmont Street, Worcester, Mass. 01605.

viously focused on the various acute problems of hemophilia, for many of which no efficacious therapy existed. At the hemophilia center in Worcester all patients attend an annual comprehensive health care clinic and long-term health data are compiled.

As a result of abnormal liver chemistries found at a recent comprehensive care clinic, the possibility that these findings might be related to the pooled, freeze-dried coagulation factor concentrates was considered. In an attempt to elucidate this point, liver chemistries were performed on a group of patients attending the Royal Free Hospital Haemophilia Center who were similar in all respects except that they were treated only with nonpooled, wet frozen cryoprecipitate prepared from the plasma of a carefully selected group of donors negative for hepatitis B surface antigen (HB_sAg). This paper reports the findings of these liver function studies, as well as a variety of unexpected abnormalities discovered in 100 unselected hemophiliacs during a 1-yr prospective study.

MATERIALS AND METHODS

Patient Population

Data were obtained from 100 consecutive patients who were seen at our hemophilia center's comprehensive care clinic in Worcester. Eighty-eight patients had hemophilia A; 12 had hemophilia B. Sixty-seven patients were classified as severe hemophiliacs (factor VIII or IX level $\leq 1\%$), 21 were moderately severe (factor VIII or IX level 1.1%–5.0%), and 12 were mild (factor VIII or IX level > 5%). Inhibitors to factor VIII were present in 6 patients and an inhibitor to factor IX was present in 1. The median age of the patients was 17 yr, with a mean of 22 yr. Nineteen patients were 10 yr of age or younger, 40 were between 11 and 20 yr of age, 31 were between 21 and 40 yr of age, and 10 were over 40 yr old.

Eighty-eight patients were enrolled in the self-therapy program; 12 were not. Various commercial factor VIII or factor IX concentrates were used by 89 patients with an average of 138 vials (approximately 250 factor VIII units or 500 factor IX units per vial) per patient per year. An additional 5 patients received only cryoprecipitate and 1 received only plasma. Five patients had no infusions during the study year, but all had received infusions in the preceding year. Complete data had also been collected on 70 of these patients for the preceding calendar year.

Additional data were obtained concurrently from the Royal Free Hospital, London, on a group of 33 English hemophiliacs. These patients were also intensively treated, but received only wet frozen cryoprecipitate prepared from selected donors who were HB_sAg negative. The mean patient age was 29. On the average, 233 bags of cryoprecipitate per patient per year were given. The mean factor VIII content of this cryoprecipitate was determined by random assay of 22 bags monthly, and it averaged 110 units per bag (range 42–128).

Methods

Serum bilirubin was performed using the method described by Malloy and Evelyn.[2] The serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were performed by the method of Henry et al.[3] The serum lactic dehydrogenase (LDH) was performed by White's method.[4] Alkaline phosphatase was determined by a modification of the method of Bessey et al.[5] The hepatitis-associated antigen (HB_sAg) was determined by radioimmunoassay (Abbott Laboratories, Chicago) and the hepatitis-associated antibody (HB_sAb) by high-voltage counterelectrophoresis.[6] Cytomegalovirus (CMV) and toxoplasmosis antibody titers were determined at Clinical Diagnostic Laboratories, Los Angeles, using immunofluorescent antibody methods.[7,8] Factor VIII or factor IX assays and assay of inhibitors to factor VIII and IX were performed using standard one-stage partial thromboplastin time–based methods.[9]

In the English study group, Hb_sAg was determined by radioimmunoassay and Hb_sAb by the passive hemagglutination technique.[10]

At the Worcester clinic, all patients received a complete physical examination by a hematology

fellow or resident, and by a staff hematologist as well. Examination of the spleen was performed in the supine and right lateral decubitus positions. It was considered enlarged only if palpable by two examiners.

Records of infusion data were kept in the Hemophilia Clinic, with additional information obtained from blood bank records. No patient received any plasma products from other sources during the study period.

Statistical analysis was performed using two-way chi square tables via the Statistical Analysis System computer analysis program, supplied by North Carolina State University, on an IBM 360–145 computer.

RESULTS

Liver Chemistries

SGOT, SGPT, and LDH levels are plotted in Fig. 1. Sixty-eight patients (69.4%) from the Worcester study group had abnormal liver function studies as recognized by an elevation of the SGOT and SGPT, or by an elevation of the SGPT alone. Levels of serum bilirubin were normal in all cases. Alkaline phosphatase was abnormal in 9 patients (9.2%), after correction for patient age. The highest level was 8.7 Bodansky units (normal <4.0).

Data were available from the preceding year's annual clinic on 68 of these 98 patients. Abnormal levels of the transaminases were present in 35 patients (51.5%). Serum bilirubin was elevated in two patients (3.9%). Of the 35 patients with abnormal liver chemistries, 15 improved, 8 failed to improve, and 12 worsened as of the 1-yr follow-up. Complete correction of abnormalities was seen in only 3 patients. (Improvement or worsening was defined as a change of more than 50% from the baseline value.) Of the 33 patients who had had normal liver chemistries at the preceding year's annual clinic, 17 had become abnormal by 1 yr later; all of these 17 patients had developed mild elevations of the SGOT or SGPT.

In the English group of 33 patients receiving only cryoprecipitate (Fig. 2), liver chemistries were abnormal in 16 (48.5%), as indicated by an increased aspartate transaminase level (>15 IU/liter). Serum bilirubin was elevated in 8 patients (23.9%), and alkaline phosphatase was increased in 9 (27.3%).

In the Worcester group of 5 patients receiving only cryoprecipitate, 3 had abnormal liver chemistries. In a group of 5 patients who received no infusions

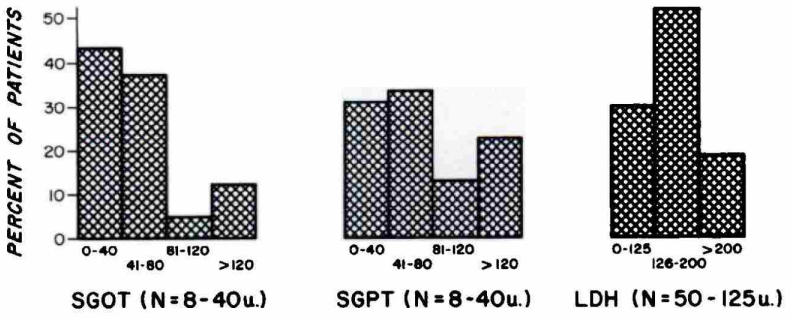

Fig. 1. Results of SGOT, SGPT, and LDH determinations from the Worcester study group of 98 hemophiliacs.

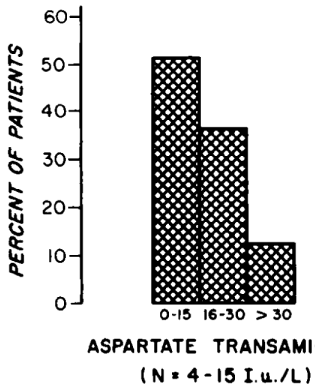

Fig. 2. Results of aspartate transaminase determination from the London study group of 33 hemophiliacs.

during the study year, 3 had abnormal liver chemistries. All of these, however, had received infusions of some plasma product during the previous calendar year.

Hepatitis-associated Antigen (HB_sAg) and Antibody (HB_sAb)

Four (4%) of the Worcester patients were positive for HB_sAg and 18 (18%) had antibodies to HB_sAg. In the English group, none was positive for HB_sAg, and 15 (46%) had the corresponding antibody.

Splenomegaly

Of 98, 26 (26.8%) of the American patients had palpable spleens. Of these 26 patients, 17 had been carefully examined for splenomegaly 1 yr earlier: 7 had had palpable spleens, 10 had not. Conversely, 3 patients had previously had palpable spleens which had disappeared by the present examination. Of 66 patients carefully examined for splenomegaly during the prior year's evaluation, 11 (16.7%) had had splenomegaly. No patients had hepatomegaly, hepatic tenderness, or physical signs of portal hypertension in either year.

Cytomegalovirus and Toxoplasmosis Antibody Titers

Antibody to CMV was assayed in the serum of 19 healthy volunteers, 9 hemophiliacs with normal liver chemistries, and 10 hemophiliacs with markedly abnormal liver chemistries. Whereas many of the normal controls showed evidence of prior CMV exposure (Fig. 3), only 1 of 19 had a titer of >1/2048. In the hemophilic group, 16 of 19 patients had a CMV titer of >1/2048. These high levels of CMV antibody were evenly divided among those hemophiliacs with and those without abnormal liver chemistries.

Improvement or worsening of liver chemistries (Table 1) did not correlate with changes in CMV antibody titer in a group of 20 patients, 10 of whom had significant abnormalities in liver function, and 10 of whom did not. Furthermore, the titer of antibody did not correlate with magnitude of exposure to plasma products.

Antibody to toxoplasma was measured in 10 hemophiliacs with markedly

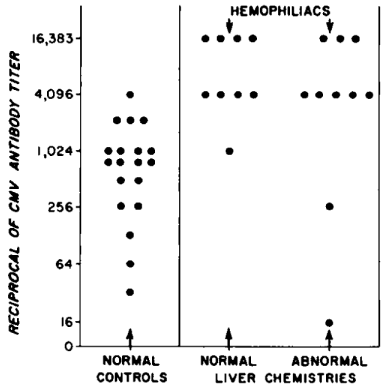

Fig. 3. Reciprocal of cytomegalovirus antibody titer in 19 healthy volunteers and 19 hemophiliacs.

abnormal liver chemistries. One patient had a titer of 1/64; the others had titers of 1/16 or less. None of these titers was considered clinically significant.

Correlation of Abnormal Liver Chemistries and Other Findings

Comparing the 30 patients with normal liver chemistries to the 68 with abnormal liver chemistries, the average age in both groups was 22 yr. The average number of infusions per patient per year in the normal group was 137 versus 120 in those with abnormal liver chemistries. HB_sAg or HB_sAb was present in

Table 1. Comparison of CMV Antibody Titers With Liver Chemistries and Infusion Frequency

Age (yr)	SGOT/SGPT		No. of Vials Infused		Reciprocal of CMV Titer	
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr
16	112/210	36/61	12	193	16384	16384
10	70/130	46/49	10	34	16384	4096
20	196/282	63/79	35	0	4096	16384
24	40/65	77/248	42	24	4096	4096
29	80/30	150/290	306	277	4096	4096
20	27/44	86/263	9	81	1024	256
18	172/181	67/93	77	254	1024	4096
9	39/20	204/114	98	132	4096	16384
48	23/25	411/910	208	237	256	4096
18	27/59	133/61	90	48	256	16
26	33/38	26/27	419	684	4096	4096
32	28/38	30/31	26	346	256	—
49	32/10	14/14	21	12	—	4096
58	18/16	5/14	60	828	1024	4096
19	—	24/32	0	85	—	16384
25	—	18/23	50*	70*	—	4096
23	—	19/27	90	187	—	16384
17	10/25	14/8	0	0	—	1024
20	24/22	23/28	108	24	—	16384
28	—	17/31	0	0	—	16384

*Units of plasma.

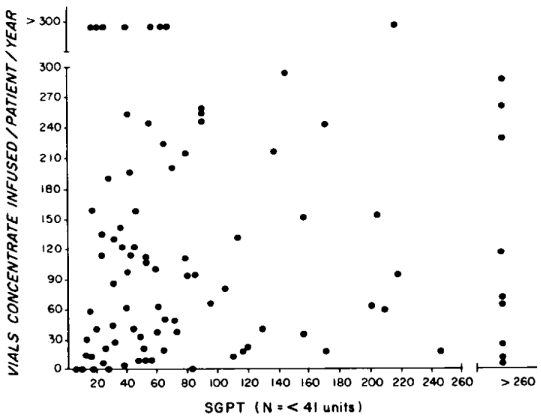

Fig. 4. Serum SGPT level in 89 American hemophiliacs plotted as a function of number of vials of clotting factor concentrate infused into each patient.

7 normal patients and 15 abnormal patients. Splenomegaly was found in 11 patients with normal liver function and in 15 with abnormal liver function. None of these correlations achieved statistical significance. There was no correlation between the presence or severity of liver function abnormalities and the time interval since the last exposure to blood products.

Correlation of Abnormal Liver Chemistries and Plasma Product Infused

In both the American and British study populations, there was no relationship between the total number of infusions given and the presence or severity of liver chemistry abnormalities, as shown in Figs. 4 and 5.

Correlation Between Splenomegaly and Other Findings

Comparing the 26 patients with splenomegaly to the 72 patients without splenomegaly, the average age in the splenomegaly group was 21 yr versus 23

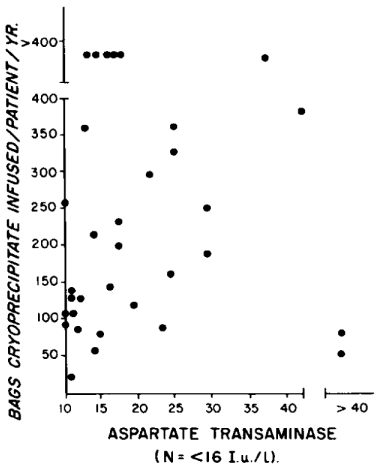

Fig. 5. Serum aspartate transaminase level in 33 British hemophiliacs plotted as a function of number of bags of cryoprecipitate infused into each patient.

yr in the nonsplenomegaly group. The average number of vials of factor VIII or factor IX concentrate infused per patient per year was 171 in the splenomegaly group and 105 in the nonsplenomegaly group. This correlation did achieve statistical significance ($p < 0.05$). Five patients with splenomegaly had received only cryoprecipitate in the study year. HB_sAg or HB_sAb was present in 6 of 26 patients with splenomegaly (23%) and 16 of 72 patients without splenomegaly (22%). Liver chemistries were abnormal in 14 patients with splenomegaly (54%) and 54 patients without (75%).

One patient had undergone emergency splenectomy following major abdominal trauma. The weight of the spleen was 150 g. The macroscopic and microscopic examination of the spleen was normal except for a small laceration and an area of pericapsular hemorrhage. This patient's spleen had not been palpable on prior physical examinations.

DISCUSSION

There have been several studies of the incidence of clinically evident hepatitis in hemophilia. Lewis[11] found an 11.7% incidence in 375 patients over a 6-yr period. Biggs[12] found a 3.8% incidence in 1737 patients over a 3-yr period. Kasper and Kipnis,[13] in 1972, found a 31% incidence of hepatitis after a first exposure to pooled factor VIII preparations.

In the American study group, we found a high prevalence (68%) of abnormal liver chemistries in the treated hemophiliacs. The abnormalities tended to persist over a 1 yr follow-up and were not correlated with age, intensity of plasma product therapy, presence of HB_sAg or HB_sAb, or CMV titer. The London treatment program, which used only nonpooled, wet frozen cryoprecipitate, yielded a somewhat lower prevalence (48.5%) of abnormal liver chemistries. These data must, however, be interpreted in the light of certain obvious differences between the American and British study groups. For example, there may be differences in the plasma donor populations. Furthermore, the intensity of therapy was not identical in the two study groups. The average American hemophiliac received 138 vials of factor VIII concentrate yearly, at approximately 250 factor VIII units per vial, representing a total of 34,500 factor VIII units yearly. The average British patient in our study received 233 bags of cryoprecipitate yearly, at approximately 110 factor VIII units per bag, representing a total of 25,630 factor VIII units yearly.

It is unfortunate that the presence of the hemostatic disorder makes elective liver biopsy difficult in these patients, thus interdicting the collection of histologic information to help explain the hepatic dysfunction. In prior studies, using the most sensitive methods available for the detection of HB_sAb, treated hemophiliacs have shown up to 80% prevalence of this antibody.[14] Chronic hepatitis virus infection, chronic CMV infection, or other infectious or noninfectious causes remain as possible explanations for the hepatic dysfunction.

A search of the literature has revealed no reports of splenomegaly associated with hemophilia. There is, however, a certain incidence of palpable spleens when apparently healthy individuals are carefully examined. In the study of McIntyre and Ebaugh,[15] involving 2200 study subjects, the incidence of splenomegaly was reported as 2.86%. At a 3-yr follow-up, 30% of these spleens had

remained palpable. More than one quarter of our patients have had palpable spleens, perhaps related in some way to the intensive therapy they received. The incidence of splenomegaly tended to increase as a function of intensity of therapy.

Splenomegaly was not correlated with age, presence or absence of abnormal liver chemistries, or presence of HB_sAg or HB_sAb. Since these patients received chronic recurrent exposure to proteins from pools of hundreds of liters of human plasma, continuous bombardment with foreign antigens may explain the splenomegaly, as may antigen-antibody complex formation. There has been experimental evidence to suggest that infusion of foreign proteins can lead to reticuloendothelial hyperplasia with the development of splenomegaly.[16,17] The absence of abdominal symptoms suggests that intrasplenic hemorrhage is not the mechanism of most splenic enlargement.

Exposure to CMV is ubiquitous, as evidenced by prior studies on the high incidence of complement-fixing antibodies in the general population.[18] Our patients had higher titers of antibodies to CMV than did a control group. Changes in titer over 12 mo did not correlate with changes in liver chemistries. CMV infection is a recognized cause of splenomegaly,[19] and could be a contributor to this finding. However, only 4 of 17 patients with CMV titers of 1/4096 or higher had palpable spleens.

CMV infection has been well documented following whole blood transfusion.[20] Leukocytes and erythrocytes are believed to harbor the virus. The high titers of CMV antibody in our patients may represent reactivation of latent CMV infection, rather than delivery of CMV in the cell-free infusion products. This hypothesis is supported by the recent work of Olding et al.,[21] who have shown that transformation of B lymphocytes by foreign antigenic stimulation results in activation and recovery of previously latent CMV from these cells.

The long-term significance of the various abnormalities reported here is unknown, and further in-depth studies are indicated. Because the abnormalities are in general not related to intensity of replacement therapy or to product used, and because the severe disability of the hemophiliac is inversely proportional to the intensity of such therapy, aggressive therapy clearly should continue.

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