Liver Dysfunction in Pennsylvania's Multitransfused Hemophiliacs

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Transaminase values [alanine amino transferase (ALT) and aspartate amino transferase (AST)] and markers for hepatitis B were serially determined in 558 hemophiliacs exposed to blood products. Hepatitis B surface antigen (HB_sAg) persistent for over 12 months was present in 6% of the patients. Antibody to hepatitis B surface antigen (anti-HBs) was noted in 90% of the 259 patients treated with factor VIII or IX concentrates but in only 49% of the 43 patients treated with fresh frozen plasma (FFP) or cryoprecipitate. Persistently abnormal transaminase values were noted in 31% of the patients treated with commercial concentrates but in only one (2%) of the patients exposed to cryoprecipitate or FFP. This difference continued even when the two groups of patients were matched for the amount of blood products, up to 50,000 units, which they had received in the study period. In the concentrate-treated patients, no correlation could be found between transaminase values and the number of units of factor VIII or IX they had received during the six years of the study (1973–1978).

Hepatitis has always represented a risk for hemophiliacs who are frequently exposed to blood products. The incidence of acute, clinical hepatitis in these patients has increased since the introduction of factor VIII or IX concentrates, particularly in patients who have received little or no prior treatment (1–3). Recently, there have been a number of publications (4–6) reporting a high incidence of chronically abnormal liver function tests in asymptomatic patients with hemophilia treated with either cryoprecipitate or concentrates.

The present study attempts to evaluate the potential adverse effects on the liver of repeated exposure to blood products in a large group of closely monitored hemophiliacs. Serial tests of serum transaminase levels and hepatitis B markers were followed over a six-year period. Data were available for all patients cared for by eight of the nine comprehensive hemophilia centers in Pennsylvania.

MATERIALS AND METHODS

Population. The medical records of 558 patients with hemophilia A, B or von Willebrand's disease who had been treated with blood products were reviewed. They had all been followed closely in the participating centers, and detailed records including serial liver function tests, hepatitis B serologies, and type and amount of therapy were abstracted. Table 1 lists the Centers and the diagnoses of patients entered into this study. Five hundred

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TABLE 1. PATIENT POPULATION*

Center	No. of patients with			
	Hemophilia			
	A	B	vW	Total
Hemophilia Treatment Center, Allentown Hospital Association	72	6	8	86
Cardeza Foundation Hemophilia Center of Jefferson Medical College	61	14	19	94
Hemophilia Project, Albert Einstein Medical Center	32	2	2	36
Hemophilia Center of Central Pennsylvania, The Milton S. Hershey Medical Center	100	5	—	105
Hemophilia Center, Children's Hospital of Philadelphia	21	—	—	21
Hemophilia Center of Western Pennsylvania, Central Blood Bank of Pittsburgh	119	32	—	151
Hemophilia Center, The Reading Hospital and Medical Center	28	5	4	37
Hemophilia Center, St. Joseph Hospital	27	—	1	28
Total number of patients	460	64	34	558

*Only treated patients are listed.

fourteen patients were treated at least once during the study period (January 1973 through December 1978). These patients are divided into those only exposed to cryoprecipitate and/or fresh frozen plasma (cryo group) and those whose treatment included commercial factor VIII and IX concentrates (concentrate group). Certain characteristics of the two groups are shown in Table 2. The cryo group is much smaller and their mean age much lower than the concentrate group. When the total treatment during the study period was calculated in units of factor VIII or IX, it was noted that in the cryo group the largest number of patients received less than 10,000 units; the reverse was found in the concentrate group.

Not all tests were performed on every patient. Table 3 lists the percent of patients that had a specific test evaluated as well as the mean age for the specific test populations.

Blood Products. Cryoprecipitate and fresh frozen plasma were prepared at local blood banks almost entirely from volunteer donors. Concentrates were purchased from pharmaceutical firms where they had been prepared from large lots of pooled plasma (> 5000 donors) primarily from paid donors. Since September 1975, only concentrates shown to be negative for HB_sAg by RIA have been used in Pennsylvania. This criterion was applied to single donor products since mid-1974 in some of the Pennsylvania centers. The total amount of treatment the patients received during their lifetime was not available, but the amount of treatment for the study period 1973–1978 could be evaluated quite accurately.

Hepatitis B Virus Markers. HB_sAg and anti-HB_s were performed by sometimes different methods in the different centers. Sensitive "third-generation tests," most often the radioimmune assays (Abbott Laboratories), but on occasion reverse passive hemagglutination methods, were used.

Hepatitis B surface antigen (HB_sAg) was performed at least once in 500 patients and at least twice in 446 patients. The mean number of tests for HB_sAg was 4.5 per patient.

Antibodies to hepatitis B surface antigen (anti-HB_s) were assayed at least once in 302 patients with a mean of 3.8 tests per patient.

Liver Function Testing. Four hundred thirty (430) patients had at least three sets of serum transaminases performed between January 1973 and December 1978. Each two sets were at least four months apart, and only sets obtained at least six months after an episode of acute clin-

TABLE 2. CHARACTERISTICS OF CRYO AND CONCENTRATE GROUPS*

	Cryo	Concentrate
Total number of patients	79	435
Mean age	11	24
Amount of treatment†		
<10	62%	21%
10–100	34%	37%
>100	4%	43%
Hemophilia A	58%	88%
Hemophilia B	13%	11%
von Willebrand's disease	29%	1%

*All patients were treated at least once during the study period (1973–1978).

†Total amount in units × 10^3 of factor VIII or IX during the study period.

TABLE 3. NUMBER OF TESTS PERFORMED IN CRYO AND CONCENTRATE GROUPS*

	Cryo group (79 patients)			*Concentrate group (435 patients)*		
	Tests performed in (%)	*Mean No. of tests/patient*	*Mean age*	*Tests performed in (%)*	*Mean No. of tests/patient*	*Mean age*
HB_sAg†	97	3.5	11	97	4.8	25
Anti-HB_s‡	54	2.84	17	59	3.47	27
Transaminase§	70	4.22	15	79	6.26	29

*All patients treated at least once within the study period (1973–1978).
†Performed at least once.
‡Performed at least once; number of tests range from 1 to 7 with approximately equal distribution.
§Performed at least three times.

ical hepatitis were evaluated. The mean number of sets of transaminase obtained on each patient was 6. Alanine aminotransferase (ALT*) and aspartate aminotransferase (AST*) were performed by various methods, having different normal ranges in the eight participating centers and results are, therefore, expressed as the relative frequency of abnormal values.

Patients were divided into three groups: those with persistently normal values, those with fluctuating levels, and those with persistently abnormal values. This last group was subdivided into those with slightly abnormal transaminases (1–2 × upper limit of normal) and those with values more than twice the upper limit of normal.

Statistical Evaluation. Standard methods (7), including nonparametric when appropriate, were employed.

RESULTS

Acute Hepatitis. Of the 546 patients with hemophilia A, B, or von Willebrand's disease for whom adequate information was available, 109 (20%) had at least one episode of clinical hepatitis with jaundice during their lifetime (Table 4). Twenty had multiple episodes resulting in a total of 135 episodes of jaundice.

To ascertain whether there was a decrease in the incidence of clinical hepatitis with jaundice after more sensitive tests, primarily RIA, have been used to screen all donors and final products; patients first exposed to concentrates in 1973–1975 were compared with those first exposed in 1976–1978 (Table 5). The difference in incidence of acute hepatitis between the two time periods was not significant for the total groups and those exposed to factor VIII concentrates. The number of patients exposed to IX concentrates is too small for comparison. Too few patients were first exposed to single donor products during the same time to obtain adequate information.

*ALT, formerly known as SGPT; AST, formerly known as SGOT.

Available information about patients listed in Tables 4 and 5 did not allow the clear separation of type of hepatitis into B or non-A, non-B in each case. However, at least two cases of HB_sAg positive hepatitis B were detected in 1977, occurring within six months of the patients' first exposures to pooled concentrate. Obviously, other patients might have acquired subclinical hepatitis and cannot be included in this comparison.

Markers for Hepatitis B. Persistent antigenemia defined as twice positive with a 12-month interval was found in 31 (7%) of the 423 patients exposed to concentrate, but in none of 77 patients treated only with cryo or FFP. In addition 19 (5%) patients in the concentrate group and 1 (1%) patient in the cryo group showed transient hepatitis B surface antigenemia.

Of the 302 patients tested for anti-HB_s, 246 (81%) were persistently positive, 6 (2%) were transiently positive, and 50 (17%) were persistently negative. Anti-HB_s, in the patients without persistent antigenemia, was positive at least transiently in 90% of patients receiving pooled products and 49% of the group exposed only to single donor products.

When the treatment groups were roughly dose matched (Table 6), the difference in anti-HB_s incidence was significant in the low- and moderate-

TABLE 4. ACUTE CLINICAL HEPATITIS WITH JAUNDICE IN PATIENTS WITH HEMOPHILIA

	No. of patients
Exposed to blood products	546
Hepatitis	109 (20%)
Once	89
Twice	15
Three	4
Four	1

TABLE 5. PATIENTS DEVELOPING CLINICAL HEPATITIS AFTER FIRST EXPOSURE TO VIII OR IX CONCENTRATES

	No. of patients exposed to			*No. of cases of hepatitis*			*%*	
Exposure (years)	*VIII*	*IX*	*Total*	*VIII*	*IX*	*Total*	*VIII*	*IX*
1973–1975	110	23	133	20	8	28	(18)	(35)
1976–1978	37	3	40	8	0	8	(22)	(0)

dose groups. For patients receiving pooled products, the incidence of anti-HB_s was significantly ($P < 0.05$) lower in the low-dose treatment group when compared to those patients receiving moderate or large amounts of treatment. In comparison, in the cryo group, no significant difference ($P > 0.05$) was noted in the incidence of anti-HB_s between the low-exposure and the moderate-exposure groups. Too few patients received over 100,000 units for adequate statistical evaluation (Table 6).

Transaminase Measurements. Table 7 summarizes the incidence of transaminase abnormalities in 430 patients with hemophilia A, hemophilia B, or von Willebrand's disease treated at least once during the study period (January 1973 through December 1978). Of the 55 patients who had received single donor products, only one (2%) had persistent abnormalities. The patients who had received concentrates were divided into those HB_sAg negative and those HB_sAg positive. In the HB_sAg negative group 27% had persistently abnormal transaminase values while in the HB_sAg positive group the number was 67%—a highly significant difference ($P < 0.01$).

No difference in the prevalence of test abnormalities was observed between patients with hemophilia A or B treated with concentrates (Table 8). Excluding patients with persistence of HB_sAg likewise did not result in a difference in test abnormalities between patients with hemophilia A and those with hemophilia B.

Relationship between Amount of Treatment and Liver Dysfunction. When the patients were divided into five groups according to the estimated total amounts of treatment expressed as units of factor VIII or IX they had received over the six years of the study period (January 1973 to December 1978), no dose-related differences in enzyme abnormalities were found in those treated with concentrates. This was observed when all transaminase determinations obtained during the study period were included (Table 9) as well as when only the last two transaminase determinations obtained in 1977 or 1978 were evaluated. Although the number of patients treated exclusively with cryo or FFP is small, there was no significant difference in transaminase abnormalities between those receiving small and those receiving moderate amounts of treatment ($P > 0.05$).

However, significant differences in liver function abnormalities were found between the concentrate and cryo groups receiving the two lowest dosage ranges ($P < 0.05$).

Persistence of Transaminase Abnormalities. Forty-two patients with elevated transaminases had received no blood products for two years. Table 10 shows that 60% of the cryo and 37% of the concentrate treated group had reverted their transaminases to normal.

In 157 patients treated yearly between 1974 and 1978 with pooled concentrate, no signficant difference in transaminase abnormalities was noted in 1975 as compared to 1978 (Table 11). As can be seen

TABLE 6. EFFECT OF AMOUNT OF TREATMENT UPON PRESENCE OF ANTI-HB_s

	43 patients treated with cryo		*259 patients treated with concentrate*		*Significance of difference*
R_x*	*No. Pts.*	*Anti-HB_s positive (%)*	*No. Pts.*	*Anti-HB_s positive (%)*	P
<10	28	43	55	71	<0.05
10–100	12	58	91	99	<0.05
>100	3	100	113	98	N.S.

*Total units of factor VIII or IX in thousands during study period 1973–1978.

TABLE 7. PATIENTS WITH HEMOPHILIA AND VON WILLEBRAND'S DISEASE

R_x product	HB_sAg in patients	Number of patients	Transaminase values*			
			N	±	1-2 × N	>2 × N
Cryo/FFP	—	55	26 (47%)	28 (51%)	1 (2%)	0
Concentrate	—	345	28 (8%)	224 (65%)	70 (20%)	25 (7%)
	+†	30	1 (3%)	9 (30%)	17 (57%)	3 (10%)

*Transaminase levels from each center were compared to that center's normal range and divided in four columns: N = always normal, ± = intermittently normal, 1-2 × N = always abnormal but never more than twice normal, and >2 × N = persistently greater than twice normal.
†Persistent > 1 year.

in the table, 67% of the patients with abnormal values in 1975 were still abnormal in 1978; however, 33% had normal values in 1978 despite continuous treatment.

Relationship between Age of Patient and Liver Dysfunction. While the number of patients in each age group is small, no significant differences in percent of patients with transaminase abnormalities in any age range were noted in either the cryo- or the concentrate-treated groups ($P > 0.05$), (Table 12).

DISCUSSION

Clinical hepatitis in hemophilia following treatment with factor VIII and/or IX concentrates has been widely recognized (1-3). While most cases of hepatitis caused by concentrate in recent years are probably of type non-A, non-B, the two cases of typical type B hepatitis reported herein are not surprising. Others have shown that eliminating all HB_sAg positive donors or processed blood products does not eliminate all cases of hepatitis B (8).

Persistence of HB_sAg for over 12 months was noted in 6% of the patients in this study as compared to 9% in a small group of hemophiliacs from the same geographical area. The prevalence of anti-HB_s in this study was significantly higher in the concentrate-treated group than in the patients treated with cryo or FFP. These findings are similar to a previous smaller study, whose patients are included in the present larger study and are from the same geographical area (4). Another study by Gerety and Barker (9), however, did not detect this difference. Their results may be different from those in this study because most of their cryo-treated group were older and had in the past received cryo prepared from plasma untested for HB_sAg.

The persistent aminotransferase abnormalities described in this and in previous studies suggest a chronic, subclinical type of liver damage in hemophiliacs who have received multiple transfusions (4-6). In fact, chronic structural changes diagnosed as chronic active hepatitis, chronic persistent hepatitis, or cirrhosis have been shown in many asymptomatic hemophiliacs (10-12). A few asymptomatic patients with normal enzyme values have also shown histologic abnormalities in their livers (12, 13). However, no biopsy series on patients with persistently normal liver function has been published to date.

The clinical and histological significance of intermittent enzyme abnormalities or persistent but minimally elevated transaminases is not known. Such abnormalities in transaminase values may be due to

TABLE 8. TRANSAMINASE ABNORMALITIES IN 369 PATIENTS TREATED WITH CONCENTRATES

	No. Pts.	Transaminase values*			
		N	±	1-2 × N	>2 × N
Hemophilia A	335	23 (7%)	209 (62%)	73 (22%)	30 (9%)
Hemophilia B	36	5 (14%)	20 (56%)	6 (17%)	5 (13%)
von Willebrand's	4	—	3 (75%)	—	1 (25%)

*Transaminase levels from each center were compared to that center's range and divided in four columns: N = always normal, ± = intermittently normal, 1-2 × N = always abnormal but never more than twice normal, and >2 × N = persistently greater than twice normal.

TABLE 9. EFFECT OF AMOUNT OF TREATMENT UPON TRANSAMINASE ABNORMALITIES

	55 patients treated with cryo/FFP				*345 patients treated with concentrates*			
		Transaminase values (%)				*Transaminase values (%)*		
R_x*	*No. Pts.*	*N*	±	*ABN*	*No. Pts.*	*N*	±	*ABN*
<10	36	55	42	3	53	15	55	30
10-50	16	44	56	—	72	7	61	32
51-100	1	—	100	—	52	8	60	32
101-500	1	—	100	—	136	5	71	24
>500	1	—	100	—	32	9	69	22

*R_X: Total units of factor VIII or IX in thousands during study period 1973-1978. Transaminase values over same period. Transaminase levels divided into: N = always normal, ± = intermittently normal, ABN = always abnormal.

repeated exposure to hepatitis viruses or to other pathological events associated with the treatment of hemophilia; they may be due to bleeding into the liver or may be unrelated to the hemophilia. Large studies involving serial biopsies as well as serologic capabilities to demonstrate non-A, or non-B hepatitis will, hopefully, be able to answer these important questions.

The percentage of patients with persistently abnormal transaminase values is slightly lower in this study than in a previous report (4). This might be due to the fact that more tests per patient have been performed in the present study as well as to the larger patient group.

The number of patients with transaminase abnormalities remained constant between 1975 and 1978, although presumably, increased sensitivity of testing methods markedly decreased HBV exposure. The amount of treatment as expressed in units of factor VIII or IX did not appear to influence the frequency of transaminase elevations. While persistent abnormality could be due to repeated exposure to non-A, non-B hepatitis viruses, the results observed in patients without exposure for over two years suggest that, in some, abnormalities are sustained by some process other than fresh virus exposure. Finally, some of the patients' abnormalities may be unrelated to treatment with blood products but may represent alcoholic liver disease or drug toxicity.

Patients with persistent HB_sAg have significantly worse liver enzyme abnormalities despite the fact that almost all of them are free of symptoms.

As in a previous study involving fewer patients (4), significantly fewer liver function abnormalities are observed in patients exposed only to single donor products than in those treated with concentrates during this study period. Of the latter many had received experimental or commercial concentrates before the study commenced. The lesser degree of liver function abnormalities in the cryo-treated group persists in those receiving up to 50,000 units over six years but seems to disappear in patients receiving more, although the numbers are too few for statistical analysis. This difference may well be due to a lesser chance of exposure to hepatitis viruses because of fewer total donor exposures in the cryoprecipitate-treated patients.

TABLE 10. TRANSAMINASE VALUES IN PATIENTS WITH PREVIOUSLY ELEVATED LEVELS BUT NOT TREATED FOR TWO YEARS

R_x product	*No. patients*	*Transaminase**		
		M	±	*ABN*
Cryo	15	9 (60%)	5	1
Concentrate	27	10 (37%)	3	14

*At least two values four months apart obtained at least 24 months after the last exposure to blood products.

TABLE 11. 157 PATIENTS TREATED YEARLY WITH CONCENTRATES*

No. of patients	*Transaminase values*		*No. of patients*
	1975	*1978*	
41 (26%)	N	N	25 (61%)
		ABN	16 (39%)
116 (74%)	ABN	N	38 (33%)
		ABN	78 (67%)

*Patients treated each year during period of 1974-1978; patients with persistent HB_s Ag excluded; first transaminase in 1975 and last one in 1978 evaluated.

TABLE 12. EFFECT OF PATIENT'S AGE UPON TRANSAMINASE ABNORMALITIES

	55 patients treated with cryo/FFP				*345 patients treated with concentrates*			
		Transaminase Values (%)				*Transaminase values (%)*		
Age	*No. Pts.*	*N*	±	*ABN*	*No. Pts.*	*N*	±	*ABN*
0–5	6	50	50	—	3	—	66	33
6–10	9	33	67	—	32	3	75	22
11–20	16	38	62	—	102	6	74	20
21–30	13	54	46	—	92	10	64	26
31–40	4	50	50	—	53	6	54	41
41–50	4	75	25	—	24	4	58	27
51–60	3	66	—	33	26	15	58	27
>60	—	—	—	—	13	15	54	31

However, it remains possible that the higher percentage of transaminase abnormalities in the concentrate-treated group might be caused by substances other than hepatitis viruses present in these blood derivatives.

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