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Scand J Haematol (1977) **18**, 214–218

Hepatitis, Type B in Haemophiliacs

Relation to the Source of Clotting Factor Concentrates

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36 children aged 3 to 18 years receiving substitution therapy for haemophilia during the period 1970 to 1976 were studied for infection with hepatitis B virus by assays for HB_sAg, anti-HB_s, and anti-HB_c. Clinical hepatitis B occurred in 3 patients (8 %) and serological evidence of infection was found in further 13 (36 %).
The occurrence of infection was associated with age but less so with the total amount of transfusion. Estimates of the risk of infection by clotting factor material of different origin indicated a figure of 1:53,000 I.U. for Danish volunteer donor preparations as well as for commercial products, the risk being apparently increased following the use of pooled blood donor material and non-Scandinavian products respectively.

Key words: haemophilia – hepatitis type B

Accepted for publication November 13, 1976

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The risk of transmitting hepatitis, type B by blood transfusion or by use of blood derivation for substitution therapy was recognized more than 30 years ago (MacCallum 1972) and hepatitis B has been found to be a major hazard in the management of haemophilia (Barker & Hoofnagle 1974). By introduction of tests for hepatitis B surface antigen (HB_sAg) as a marker of potential infectivity and elimination of antigen-positive blood donors the risk has been reduced (Senior et al 1974). The most dangerous sources of infection may also be eliminated by avoidance of paid blood donors, but some cases of hepatitis B still occur in the blood recipients in spite of these precautions (Alter et al 1972). For evaluation of the present risk of infection we have followed a group of young haemophiliacs treated with transfusion and factor concentrates of various origin and compared the incidence of serological or clinical hepatitis which this treatment produced.

MATERIALS AND METHODS

36 boys aged 3 to 18 years with moderate or severe type A or B haemophilia, i.e. patients with

TABLE 1

Patients studied, therapeutic material used, and the occurrence of hepatitis infection according to age

Age group (years)	No. of patients	Substitution therapy given (I.U.)		Single donor origin (%)	Hepatitis B infection No. positiv for:			Hepatitis non-B No. of patients
		Mean	(Range)		HB_sAg	anti-HB_s	anti-HB_c*	
3– 5	6	20,600	(80–55,000)	99	0	0	0	0
6– 9	12	21,800	(3000–50,000)	65	1	2	2	1
10–13	7	35,087	(3000–75,000)	38	0	4	5	1
14–18	11	20,160	(80–55,000)	93	2	5	4	0
Total	36	23,800	(80–75,000)	73	3	11	11	2

* 5 patients, 2 of whom were anti-HB_s positive, were not studied.

TABLE 2

Risk of infection following different types of therapeutical material according to assumed source

Origin of clotting factor products	No. of patients treated	Total amount given (I.U.)	No. of hepatitis B infections (according to assumed origin)	Calculated infection rate	
Danish single donor	33	618,000	10	1:61,800	
Danish pooled donor	7	6,300	1	1: 6,300	1:57,000
Commercial:					
Scandinavian origin	6	211,000	3	1:70,300	
Overseas	3	13,700	2	1: 6,800	1:45,000
Total	36	849,000	16	1:53,000	

TABLE 3

Risk of infection following different types of therapeutical material according to calculated infection rates

Group	No. of patients	Total amount given (I.U.)	No. of hepatitis B infections observed (calculated)	Calculated infection rate
Danish blood donor products only	27	515,000	10	1:51,500
Danish blood donor products and commercial factor concentrates	9	108,000	(2.0)	–
		225,000	6 (4.0)	1:56,000

a clotting factor concentration less than 5 % of normal value, were treated and regularly seen in the department of pediatrics during the period 1970–1976 were studied.

According to the origin of the substitution treatment the patients could be classified in 3 groups:

I. 20 patients who received blood or plasma derivates from single donor units only.

II. 7 patients who received factor concentrates from pooled blood donor units in addition to single donor units.

The blood donations for both these groups originated from Danish volunteer donors, who had been screened for HB_sAg by counter immunoelectrophoresis (CIE) prior to each donation throughout the period 1970–1976.

III. 9 patients who in addition to the therapy given to group II, had received commercially produced foreign factor concentrates (manufactured by Hyland, Abott, Kabi, and 'Finnish Red Cross Blood Service').

For comparison of the treatment given to the different patients the transfusions were expressed in international clotting factor units (I.U.): 200 ml plasma being equal to 80 I.U. (Bloodbank department, personal communication).

Screening for hepatitis comprised clinical examination and determination of GPT, bilirubin, and investigation for HB_sAg by CIE and radioimmunoassay (Skinhøj & Hansen 1973) at least once during each admission.

From patients admitted to local hospitals for emergencies, detailed records were obtained regarding the substitution therapy given and evidence of hepatitis.

Subclinical infections was identified by investigation of serum samples for anti-HB_s and anti-HB_c.

The investigation for anti-HB_s was performed by a radioimmunoprecipitation assay as described previously (Skinhøj & Hansen 1973).

Anti-HB_c was detected by a CIE technique described elsewhere (Skinhøj & Thulstrup 1971) using purified HB_cAg kindly donated by Dr. B. G. Hansson, Malmö, Sweden.

The electrophoresis was run for 2 h in a 0.9 % agarose-agargel, and the plates were read after overnight incubation without further treatment.

RESULTS

The distribution of the 36 patients according to age of infection or last time of study, respectively, is given in Table 1 together with basic data of substitution therapy and occurrence of hepatitis infection.

Clinically overt icteric HB_sAg positive hepatitis occurred in 3 cases (ages 9, 13, and 15 years). Anti-HB_s was detected in 11 children without evidence of infection.

A further 2 asymptomatic children were also found to be positive for anti-HB_c. The correlation of these 16 cases of hepatitis B infections to the age and to the amount of substitution therapy is given in Figures 1 and 2.

In 2 children a clinical hepatitis occurred, which was negative for HB_sAg by radioimmunoassay and the hepatitis B associated antibodies.

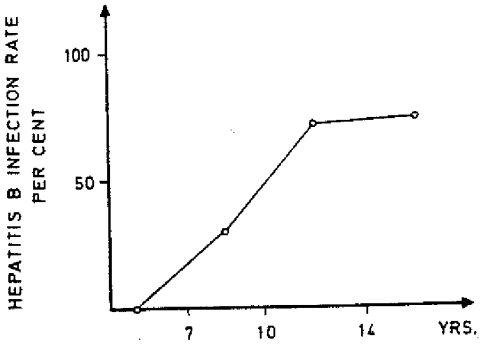

Figure 1. Hepatitis B infection rate in relation to age.

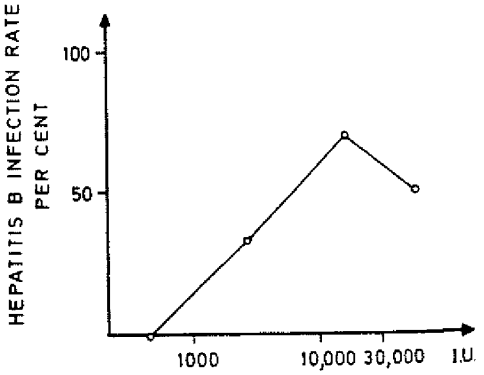

Figure 2. Hepatitis B infection rate in relation to amount of therapeutic material used.

No difference in risk of hepatitis B infection was found between patients with haemophilia A and B. The figures being 13 out of 30 and 3 out of 6 cases, respectively. Neither was infection correlated to the presence of inhibitory factor (3 children).

The relation of infection to the type and the source of therapy was assessed by 2 methods. In Table 2 the infected patients were allocated according to the assumed origin of infection, i.e. for the clinical cases the material given 1½ to 5 months prior to onset of disease and for the anti-HB_s or anti-HB_c positive patients the type of treatment given before the detection of antibody.

The second approach was to calculate the risk of infection in patients only given Danish preparations and subtract the calculated number of 'Danish infections' from the total number observed in the group receiving Danish as well as foreign preparations in order to obtain a figure for the commercial products (Table 3).

By both methods the risk of infection was found to be close to 1:53,000 I.U. and no difference between Danish and foreign commercial preparations was found. Although not statistically significant, a ten-fold difference in the calculated infection risk was found between single donor units and pooled preparations of Danish origin and between commercial products from different countries (Table 2).

For the 2 cases of non B-hepatitis the origin of infection in 1 case was presumably a commercial factor concentrate while in the other multiple types of treatment were given prior to the infection.

DISCUSSION

A history of clinical hepatitis in haemophiliacs has been found in a few to 20 % of severely affected adult patients (Briggs 1974, Lewis et al 1974, Mannucci et al 1975). However, many more patients have evidence of infection when serologically evaluated. The prevalence of anti-HB_s as detectable by haemagglutination or radioimmunological assays in adult patients ranges from 60–100 % (Peterson et al 1973, Burrell et al 1974, Hoofnagle et al 1975).

The presence of anti-HB_s in these patients could possibly reflect repeated exposure to inactivated viral material rather than past infection with hepatitis B virus.

However, Hoofnagle et al (1975) and Hansson (personal communication) demonstrated that anti-HB_s positive patients usually also had antibody to hepatitis B core antigen (anti-HB_c), and this antibody is considered only to develop following viral replication (Krugman et al 1974).

In the present study the close correlation of the 2 antibodies was confirmed and the presence of either antibody was regarded as evidence of infection. Hence, the overall hepatitis B infection rate in the present series of patients comprised 45 %, one fifth of the cases being clinically overt.

The calculations on the risk of infection following substitution therapy of various origins indicated that material from Danish volunteer donors carried an estimated risk of 1:55,000 I.U. equal to exposure to 800 donors. Such a hepatitis B virus carrier rate is rather similar to that calculated for volunteer donors in the U.S.A. (Grady et al 1972) and England (Zuckerman et al 1974). Apparently the screening of the donors for HB_sAg initiated in 1970 has not yet eliminated the pool of infectious donors.

Rather unexpectedly in our material, the commercial clotting factor preparations did

not show a higher risk of infection although this material is derived from large pools of donors. However, most of the preparations used were of Scandinavian origin and hence derived from donors with a low hepatitis B carrier rate.

The observation that pooled products of Danish origin appeared more infectious than single donor preparations and that the country of origin may influence the risk carried by the commercial products is in accordance with previous studies (Barker & Hoofnagle 1974, Lewis et al 1974) and supports the desire for an extended use of products based on volunteer single donor plasmas.

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A. J. Zuckerman. Shortly after the introduction of sensitive techniques for screening blood donors for hepatitis B surface antigen, it became apparent that the transmission of hepatitis B by transfusion of blood and blood products was reduced but not abolished [1, 2]. In the course of a number of recent surveys of posttransfusion hepatitis, only a relatively small proportion of patients had serological evidence of exposure to hepatitis B virus. However, sensitive tests such as radioimmunoprecipitation for hepatitis B core antibody [3] have not been used in these studies and the potential value of such screening procedures may have been, in general, underestimated. A sensitive test for core antibody may be an indicator of continuing replication of hepatitis B virus. A recent investigation [4] demonstrated that examination for surface antigen and surface antibody only may yield negative results during the early phase of convalescence from hepatitis B, and in this study of an outbreak of hepatitis B associated with transfusion of plasma protein fraction core antibody alone was found in 23% of patients with posttransfusion infection. The value of screening blood donors for core antibody merits further investigation.

It has also become apparent as a result of a number of recent studies of posttransfusion hepatitis that only a relatively small number of patients suffered from hepatitis B. Epidemiological and serological evidence was obtained that hepatitis A, EB virus or cytomegalovirus were not implicated.

Other evidence that an agent other than type B hepatitis may be transmitted by blood was provided by a report of an outbreak of short-incubation non-B hepatitis and hepatitis B in southern England associated with the use of 3 of 4 batches of a commercial factor VIII concentrate. Details of a non-B acute hepatitis outbreak in a hemodialysis unit in London have also been published. And in studies of hepatitis in an endemic zone in Costa Rica, evidence was provided for viral hepatitis other than type A or type B which was not associated with blood transfusion. In that study EB virus and CMV infection were excluded in all but one of the patients.

It is evident from these studies that there is a third and possibly other types of human hepatitis viruses, but there are as yet no precise virological criteria or specific tests for these agents.

Vox Sang. 32: 346 - 363 (1977)

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