Antibody to hepatitis B antigen in haemophiliacs and their household contacts

C. J. BURRELL, A. C. PARKER, D. M. RAMSAY, AND ELAINE PROUDFOOT

From the Department of Bacteriology, Edinburgh University Medical School, Edinburgh, and the Department of Haematology, Royal Infirmary, Edinburgh

SYNOPSIS The prevalence of antibody to hepatitis B antigen, detectable by radioimmunoassay, was found to be no higher among 58 long-term household contacts of multiply transfused haemophiliacs than among 100 randomly chosen blood donors. This suggested that such contacts do not have greater exposure to serum hepatitis virus than that occurring through natural means. Among those persons possessing antibody, the multiply transfused haemophiliacs showed a marked tendency for higher antibody titres than their contacts, implying differences in pathogenesis between infection acquired through multiple transfusion and infection acquired naturally.

The presence of antibody to hepatitis B antigen (HB Ag) is considered on epidemiological grounds to be an indication of previous infection with serum hepatitis virus. Using the sensitive techniques of passive haemagglutination or radioimmunoassay for detection of antibody, recent serological surveys have suggested that subclinical infection may be a common event. It has been possible to relate this to known risk factors such as multiple transfusion with blood or blood products and contact with renal dialysis units or institutions for the mentally retarded (Lander, Alter, and Purcell, 1971; Szmuness, Prince, Etling, and Pick, 1972; Pattison, Maynard, Berquist, and Webster, 1973). As a corollary to this, means of transmission of the disease other than skin penetration are being increasingly implicated, including close physical contact (Heathcote and Sherlock, 1973; Fulford, Dane, Catterall, Woof, and Denning, 1973) and, perhaps exceptionally, aerosol spread (Almeida, Kulatilake, Mackay, Shackman, and Chisholm, 1971). To extend observations to another group possibly at risk, we have examined the long-term household contacts of haemophiliacs attending the Edinburgh Haemophilia Reference Centre. Evidence is now presented that such contacts do not have a higher prevalence of antibody to HB Ag than that occurring in a control population at large.

Methods and Results

Haemophiliacs were classified as severely affected

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(plasma factor VIII or IX < 1%) and others (plasma factor VIII or IX > 1%). Those in the severely affected group had received transfusions on at least nine occasions before the study, in most cases considerably more, while the others had mainly required replacement for elective procedures and their transfusion rates were comparatively low. Regular blood donor screening for HB Ag by countercurrent immunoelectrophoresis (CIEOP, Prince and Burke, 1970) began in Edinburgh in February 1971. Almost all the transfused haemophiliacs in this study had received untested blood or blood products before that date. The household contacts of each haemophiliac were classified as wife (genetically unrelated), or mother, or other genetically related contact.

Only one of the 46 haemophiliacs and none of the 58 contacts were positive for HB Ag by the CIEOP test; this haemophiliac was a known long-term carrier of HB Ag with persistently elevated serum glutamic-oxaloacetic transaminase levels but no

	Positive	Total
Total haemophiliacs	17 (36.9%)	46
Severely affected haemophiliacs	15 (55.5%)	27
Other haemophiliacs	2 (10.5%)	19
Total contacts	10 (17.2%)	58
Wives	0 (0)	9
Mothers	4 (19.0%)	21
Other contacts	6 (21.4%)	28
Blood donors	16 (16%)	100

Table I *Prevalence of antibody to HB Ag, detectable by radioimmunoassay among the various groups studied*

	Antibody Titre			
	30 - 216	216 - 1296	1296 - 38 880	> 38 880
Total haemophiliacs	3	5	7	2
Total contacts	6	3	1	-
Mothers	3	-	1	-
Other contacts	3	3	-	-

Table II Distribution of titres of antibody to HB Ag among the haemophiliacs and their contacts

other evidence of liver dysfunction. Three of the haemophiliacs and five of the contacts gave a past history of jaundice.

In order to obtain a more sensitive indication of the spread of infection, the groups were also tested for antibody to HB Ag. Sera were taken from each haemophiliac and his household contacts at the same time when possible, and examined for antibody to HB Ag by a double antibody radioimmunoassay (Lander *et al.*, 1971; Hollinger, Vorndam, and Dreesman, 1971). Sera diluted 1 in 20 in phosphate-buffered saline containing 0.5% bovine serum albumin were incubated for two days at 4° in the presence of ¹²⁵I labelled HB Ag (approximately 3 ng HB Ag protein), and for a further 16 hr at 4° after the addition of rabbit antihuman IgG. The remaining steps in the procedure were as described for the radioimmunoassay of HB Ag (Burrell, Proudfoot, Keen, and Marmion, 1973). Labelled HB Ag subtype 'ay' was used, since preliminary results had indicated that antibodies to this subtype were commoner in Edinburgh than antibodies to subtype 'ad'. Test sera precipitating greater than 15% labelled HB Ag were considered positive for antibody; this figure lay well outside 3 standard deviations from the mean of six negative control sera, which precipitated from 7 to 12% with different preparations of labelled HB Ag.

The prevalence of antibody to HB Ag among the groups studied in comparison with 100 randomly chosen volunteer blood donors is shown in table I. A significantly greater prevalence of antibody was found in the total haemophiliacs compared to both the total household contacts (0.01 > *p* > 0.001) and the blood donors (*p* < 0.001), while no difference was seen between total household contacts and random blood donors (*p* > 0.5). In particular wives did not appear to be at special risk, although the numbers in this group were small. The prevalence of antibody among the haemophiliacs was greatest in that group receiving regular transfusion. The antibody-positive sera were then titrated and grouped according to their titres (table II); the distribution of antibody titres among the haemophiliacs was markedly slanted towards high titres, while low titres were commoner among their contacts.

Discussion

Our findings confirm the report of Lander *et al.* (1971) showing a higher prevalence of antibody to HB Ag among multiply transfused persons than among blood donors. On the other hand, long-term contacts of these patients did not have a significantly higher antibody prevalence than voluntary blood donors, suggesting that household contact with multiply transfused persons does not lead to a higher rate of subclinical serum hepatitis infection than that occurring endemically in the general population.

The distribution of antibody titres is of particular interest. High titre antibodies, detectable by CIEOP, have often been noted among multiply transfused patients. Our results demonstrate a marked tendency for high titres in this group compared with patients acquiring infection through natural means when low titre antibodies appear the most usual occurrence. This may be due to repeated subclinical infections with serum hepatitis or to repeated active immunization with non-replicating antigenic material. Further knowledge of the pathogenesis of serum hepatitis should help to clarify this point.

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