Antibody to Hepatitis B surface antigen in haemophiliacs on long-term therapy with British plasma FCS

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Summary

Thirty five patients with haemophilia A were studied clinically and serologically between 1971-1972 and 1975-1976 for evidence of hepatitis B infection. One patient suffered from clinical hepatitis B, and a further 8 patients showed antibody response to hepatitis B surface antigen (HBsAg) consistent with exposure to HBsAg during this period. In 14 patients no evidence for HBsAg exposure was found, while the remaining 12 patients showed high titres of antibody to HBsAg at both times and no inference could be drawn regarding HBsAg exposure. All patients had received exclusively replacement Factor VIII material prepared within one local centre from HBsAg-screened volunteer Scottish blood donations. It was possible to calculate from the details of the therapy given that the rate of HBsAg seroconversion in these patients represented approximately 0.3 HBsAg-containing donations/1,000 donations.
Introduction

The presence of hepatitis B surface antigen (HBsAg), or the development of antibodies to hepatitis B core antigen (anti-HBc) or to HBeAg (anti-HBe), are currently the most reliable serological markers of hepatitis B virus (HBV) infection (Goldin et al., 1977). Of these, the two former reactions almost invariably indicate ongoing or past virus replication; the development of the more long-lasting anti-HBs (or a " winnem" into HBS) may indicate either infection or active immunisation with HBsAg. Surveys of the prevalence of anti-HBs in healthy transfused haemophilies have confirmed the high rates of exposure to HBsAg that have occurred in such patients (Fenster, 1963; Iwata et al., 1971; Burrell et al., 1977; Burrell and Fenster, 1980), although such patients rarely develop clinical hepatitis (Iwata, 1974). The introduction of universal blood donor screening for HBsAg has substantially reduced but not eliminated post-transfusion hepatitis B infection (Goldfield et al., 1975) but the continuing risk of HBV infection for haemophilies is difficult to assess. This is due in part to the widespread use of commercial replacement materials prepared from a variety of sources and to the difficulty in accurate documentation of the sources of all materials administered.

In a previous study (Burrell et al., 1974) we reported that 17 (36.5%) of 47 haemophilies attending the Edinburgh Haemophilia Reference Centre in 1972 were positive for anti-HBc using a radio-immunoprecipitation assay. In that study, those haemophilies
who required the most frequent therapy showed the highest antibody prevalence (15 positive out of 27 = 55.5%). Patients attending the centre received only replacement material from the Edinburgh Blood Transfusion Centre, prepared exclusively from volunteer blood donations collected and tested for HBsAg at the various Scottish Blood Transfusion Centres before forwarding to Edinburgh. HBsAg testing was not done routinely since 1971, firstly by counter-current immunoelectrophoresis and more recently by haemagglutination inhibition (HAI: N Value 16, 1974), reverse passive haemagglutination (RPHA: Immens Laboratories), or radioimmunoassay (RIA: Ausab). Daily positive donations, which in different Scottish regions range from 0.2 - 1.5/1000 donations (J. Lepins, personal communication; see table I on the other hand anti-HBc positive donations (23/1000) detected by radioimmunoassay for the Edinburgh region (Carroll, Lepins, Forwood, Gallowton, Cram, Rochebroch, Jure, Harte and Lumsden, 1974) are not included. This situation has provided a unique opportunity to study hepatitis B seroconversion rates in patients coming into contact with fractions from large numbers of volunteer plasma donations, prepared within one centre, since the institution of universal HBsAg screening. We report a study of selected haemophiliacs over the period 1971-72 to 1975-76 with respect to the development of anti-HBs and an attempt to relate the findings to the type and frequency of replacement Factor VIII therapy given during this period.
Methods and Results

Thirty five haemophili A patients were included in the survey. A serum sample was taken from each patient taken between April, 1971 and June, 1972, and again between July, 1972 and March, 1976 and stored at -20°C. These sera were examined at the same time (1976) for HBsAg by RPA and for antibody to HBsAg (anti-HBs) by radioimmunoprecipitation (Russell et al., 1974). During this period one patient only suffered from clinical HBsAg positive hepatitis and subsequently convalesced to anti-HBs positive (see below). Liver function tests were carried out at irregular intervals on most of the patients, but no biochemical evidence of additional acute infections was found. All patients except those received varying amounts of replacement therapy during the period; this was given either as cryoprecipitate (FSH, Herschfield and Pappenheimer, 1964), as anti-immunoglobulin factor (A.I.F.: Bieneck, Bieneck, Jopson and Clinton, 1968), or as anti-intermediate A.I.F. (A.I.A.H.F.: Neuman, Johnson, Roper in and Furcht, 1971; James and Vickerhausser, 1972).

At both sampling times, all patients were negative for HBsAg by R.P.A. and 20 (57%) of the 35 patients were anti-HBs positive. Twelve patients remained anti-HBs positive with unchanging high titres during the study period; no inferences could be made about the effect of therapy on their antibody state. The remaining 23 patients could be grouped as (1) Anti-HBs positive in 1971-1972 and negative in 1975-1976 (2) Anti-HBs negative on both occasions (3) Anti-HBs negative in 1971-1972 and positive in 1975-1976.
(4) Anti-HBs positive on both occasions with a hundred-fold or greater increase in antibody titre between the two sampling periods.

In considering the interpretation of these changes in terms of exposure to HBV, it seemed possible that patients in group (2) (no titre to high titre, might have developed, and subsequently lost, short-term antibodies during the study period; eight sera from 14 of these patients were available at the beginning, three were available, and three each - one was found to be anti-HBs positive. Consequently, when the one was considered to have been exposed to HBV. While a much more comprehensive study of the various groups and the correlation of clinical tests and exposure to HBV

three of the 14 patients without evidence of exposure to HBsAg had not titre to high titre during the study period; one was

was then examined in detail (table II): records were available of all

conversions and 11 patients without evidence of exposure, was

preparations anticipated (including batch numbers for A.R.T. and

exposure tended to have received less therapy but there was no

40 and 600 donations respectively, it was possible to calculate the
total number of donation-exposures for each patient. After allowing
for 13 batches of A.H.F. and 9 batches of N.I.A.H.P. which were
given to more than one patient (usually two), it was calculated
that the u. groups of patients combined had received 3256
different batches of cryoprecipitate, 235 different batches of A.H.F.
(1,124 donors) and 27 different batches of N.I.A.H.P. (16,200 donors),
presenting exposure to a total of approximately 23,700 donors.

In 5 conversion events recorded among recipients of this material,
at least 5 of these donations must have contained HBaG, i.e., one
positive donation in every 5,400 or 1.7 positive donation/1,000
donations.

Discussion

The anti-HBs conversion events recorded here may have
resulted after infection with hepatitis B virus or after active
immunization with anti-HBs-positive material; serological distinction
between these two alternatives (e.g., by regular testing for HBaG
and anti-HBs) was not possible. Patients without evidence of
exposure may include poor antibody responders or individuals with
a short-lived anti-HBs response after contact with positive material.
Indeed, the disappearance of detectable anti-HBs between the two
combing times in 6 patients described here, provided clear evidence
that such antibody need not persist for life, and that surveys of anti-
HBs prevalence at one time point will not identify all those who have
suffered past HBV infection.

In a study in New Jersey, U.S.A. of the recipients of whole
blood transfusion after screening for HBaG by radioimmunoassay,
4,7/1,000 volunteer donations and 8.7/1,000 commercial donations
produced serological evidence of HBaG exposure (Goldfield et al.,
1975). Overall HBaG carrier rates in volunteer blood donors
and lower in Scotland (0.2-2.25/1,000 by HAI or IIA) than in New Jersey (1.5/1,000 by PMA); the difference in anti-HBc prevalence with (PMA), i.e., retrospectively by (7) my earlier differences in the frequency of infected HBs antigen in the two populations. However, when interpreting the above data of 0.7 HBs-antigen-containing donations/1,000 electrophoresis donors, one cannot ignore the present findings in this study. Other, additional factors must be considered.

2) The lower of 0.7 (HBs antigen-containing donations/1,000 after HBs antigen testing) may be lower than the true rate of HBs antigen-containing donations, since (a) patients in the community may have received more than one positive unit, (b) patients with an A.H.F. and I.H.F. may have obtained more than one contaminated donation, and (c) the number of anti-HBc in patients with chronic HBs antigen or reactive A.H.F. or I.I.A.H.F. may have initially fluctuated during infection (but not necessarily immunity) of the preparation.

3) The levels of dilution of the HBs antigen in one positive donation varied significantly according to the levels of precipitate (red cell size 2-3) or H.I.A.H.F. (red cell size 3-4) used, and according to the unknown extent of selective concentration or removal of HBs antigen and infectious virus during fractionation of the different preparations. Thus the quantitites of viral material administered may not be strictly comparable to whole blood transfusion.

3) Many patients in this survey received repeated treatments with the same batch of material, separated by hours, days, or weeks; HBV infection might be favoured by one large dose, whereas active immunization should be favoured by repeated antigenic stimuli of adequate size. The effects of these factors on seroconversion rates could not be examined in the present study.
A Finnish study of 36 children with haemophilia A or B receiving replacement therapy from various sources revealed serological evidence for HDV exposure in the period 1970-76 (Soini et al., Tinkham and Cohen, 1977). This represented an overall rate of 1.5% HDV-positive donations/1,000 donations-exposures. Observations suggested that both leishman volunteer and commercial plasma donor preparations involved a similar risk, which was associated with the use of pooled donor material from either source. However, the inclusion of haemophilia B patients in these studies and the use of preparations from several sources in some of the patients have introduced additional variables to those in our survey.

Finally, our findings should not be extrapolated to represent the true rate of HDV infection in the donor population after HDV screening. Instead, they should provide a guide to the likelihood of cross-infection to anti-HD positivity after factor VIII replacement from multiple defined sources, and a basis for comparison of this material with commercial factor VIII preparations.
Acknowledgements

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References


References (continued)


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<th>Sero logical events</th>
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<th>Conclusions regarding exposure to HBsAg positive material</th>
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Table I Classification of patients according to changes in anti-HBs reactivity.
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<th>Patients who seroconverted</th>
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*HBsAg positive 29/12/77; negative 14/9/75

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| 3813 | 41 | 2300 | 4 | 1900 | 7443 |

Table II Details of therapy received by patients in the groups indicated during the period of study.