Sex differences in response to hepatitis B infection among patients receiving chronic dialysis treatment
[hepatitis B virus/hemodialysis/surface antigen of hepatitis B virus (HBsAg)/antibody to hepatitis B surface antigen (anti-HBs)/
chronic liver disease]

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Communicated by Baruch S. Blumberg, April 7, 1977.

ABSTRACT Patients undergoing treatment at a community-based renal dialysis clinic were monitored monthly for hepatitis B surface antigen (HBsAg) and antibody to HBsAg (anti-HBs). Of 160 patients who began treatment HBsAg(−)/anti-HBs(−), 77 subsequently became HBsAg(+). Once HBsAg(+), males were more likely to remain HBsAg(+) indefinitely, whereas females were more likely to convert to HBsAg(−) and develop anti-HBs. This was not due to a sex difference in exposure to hepatitis B virus because only patients who became infected while undergoing treatment were included in the analysis. These data are clear evidence of a true sex difference in response to hepatitis B virus, which may partially explain the greater incidence of several chronic liver diseases, including primary hepatocellular carcinoma, in males.

In most populations the prevalence of chronic carriers of the hepatitis B virus (HBV) is greater in males than females. This sex difference was reported in 1966 by Blumberg et al. in three tropical populations (1) and subsequently confirmed by many investigators in studies of blood donor populations (2–8), various hospitalized and non-hospitalized populations (9–11), kidney transplant and chronic hemodialysis patients (12), and residents of institutions for the mentally retarded (13, 14). Some exceptions to this pattern have been observed (9), including a study in Greece in which the frequency of detection of the surface antigen of HBV (HBsAg) was higher (but not significantly) in females (15).

The prevalences of several HBV-related chronic liver diseases such as chronic active hepatitis, post-necrotic cirrhosis, and primary hepatocellular carcinoma are also greater in males (16–19). Chronic active hepatitis is of particular interest because one form, lupoid hepatitis, is more frequent in females, but HBsAg(+) chronic hepatitis is more frequent in males (20, 21).

There are fewer reports on the prevalence of antibody to HBsAg (anti-HBs) by sex, but most investigators have not found significant sex differences (22–25). Tevaluo-Aarnio et al. found a greater frequency of anti-HBs in male residents of a Finnish institution for the mentally retarded (26). Mazzur and Jones (24) and Vierucci et al. (25) reported frequencies of anti-HBs relative to the frequencies of HBsAg. Mazzur did not detect a sex difference in the ratio of HBsAg to anti-HBs on the island of Santa Cruz in the New Hebrides, but Vierucci observed that among multiply transfused children with thalassemia, females were more likely to have anti-HBs than HBsAg, whereas males were equally likely to have either.

In most studies it is difficult to determine whether sex differences in HBsAg and anti-HBs prevalences are due to sex differences in response or exposure to HBV. Mazzur has suggested that difference in exposure is the case in populations where sex differences in HBsAg or anti-HBs are observed (24).

None of the reported studies of populations analyzed the responses of individual members of the population with respect to the precise time course of HBsAg and anti-HBs.

The purpose of this report is to test, in a group of chronic hemodialysis patients, the null hypothesis that with equal exposure there is no sex difference in response to HBV. The analysis involves only patients who began hemodialysis treatment without detectable HBsAg or anti-HBs and subsequently acquired HBsAg. Because all patients are infected, any differences detected in persistence of HBsAg, or development of anti-HBs, must be due to differences in response.

MATERIALS AND METHODS

Serum samples from patients undergoing chronic hemodialysis at a community-based chronic dialysis clinic in Philadelphia were tested monthly for presence of HBsAg and anti-HBs. The patient population and methods for detecting HBsAg and anti-HBs have been described in detail previously (27). Sera were screened initially for HBsAg by counter electrophoresis (28) and immunodiffusion (29) and for anti-HBs by passive hemagglutination (30). To determine the precise times of development and loss of HBsAg, serum samples that were HBsAg(−) and anti-HBs(−) by the above tests were tested by radioimmunoassay (Austria II) (31).

Analyses similar to life tables were used to estimate the persistence of HBsAg and development of anti-HBs. Differences between survival curves were determined by the method of Thomas and Crunkemier (32). Mean ages were compared by the Mann-Whitney U test (33, pp. 116–127), and frequencies of seroconversion to HBsAg were compared by the 2 × 2 χ² statistic (33, pp. 196–202). Data were entered on computer cards, stored, and processed in a Hewlett-Packard minicomputer.

RESULTS

Between November 1970 and October 1974, 160 patients began dialysis treatment without HBsAg or anti-HBs. Seventy-seven of these patients became HBsAg(+). The frequency of seroconversion to HBsAg(+) was higher in males (49/94, 52%) than females (28/66, 42%), but the difference was not significant.

Fig. 1 shows the probability of remaining HBsAg(+) "indefinitely" once a patient has been HBsAg(+) for n months. Males were significantly more likely to remain HBsAg(+) indefinitely (i.e., become chronic carriers) than females. This sex difference was detectable until a patient had been HBsAg(+) for 13 months and was significant for 8 months.

In addition to being less likely to become HBsAg(−), males were also less likely to develop protective titers of anti-HBs. The probabilities of remaining anti-HBs(−) were significantly different 2, 3, and 8 months after becoming HBsAg(+) (Fig. 2). Three patients, two females and one male, became

Abbreviations: HBV, hepatitis B virus; HBsAg, surface antigen of HBV; anti-HBs, antibody to HBsAg.
HBsAg(−) without subsequently developing detectable levels of anti-HBs.

Fig. 3 shows the distribution of ages by sex for the patients studied. No significant age difference between males and females was found. We also compared mean ages according to sex and response to HBV and again found no significant differences. Previously, we reported that there was no association between the type of underlying renal disease and the persistence of HBsAg or the development of anti-HBs (27).

**DISCUSSION**

These data require rejection of the null hypothesis that sex differences in HBsAg and anti-HBs prevalences in hemodialysis patients are not due to sex differences in response to HBV infection. Among 77 patients infected with HBV while undergoing treatment at a single dialysis clinic, males were significantly more likely to remain HBsAg(+), whereas females were more likely to develop anti-HBs in response to HBV infection. This difference was not related to sex differences in age or rate of infection. Therefore, it is likely that males (at least those with chronic renal disease) are more susceptible to becoming chronic carriers of HBV and differ from females in their immune response to the virus.

Recently, we reported that recipients of kidney transplants who were anti-HBs(+) prior to surgery had early graft rejection, whereas chronic carriers had delayed rejection. Grafts from male donors were particularly at risk; eight of nine were rejected by patients with anti-HBs within 4 months of transplantation (34).

These observations, in conjunction with the data reported here, suggest the hypothesis that there is a similarity (cross-reactivity) between HBsAg and an antigen on the surface of male cells. Whether or not this is the mechanism of susceptibility, the fact that males are likely to retain the virus longer than females may contribute to the greater risk males have of developing the chronic liver diseases associated with hepatitis B infection. That is, males are more likely to become chronic carriers of HBV and as a consequence more likely to develop

![Fig. 1. The probability of male or female patients remaining HBsAg(+) indefinitely once detected positive. The numbers in parentheses are the numbers of patients at risk at each time interval. A male dialysis patient who is HBsAg(+) on a single test has a 68% chance of remaining HBsAg(+) indefinitely, whereas the probability for a female patient is 33%. Significance levels for differences between the sexes are shown in the arrows between the curves, as calculated by the method of Thomas and Grunkemeier (32). The longer a patient is HBsAg(+), the greater his or her chance of remaining HBsAg(+).](image1)

![Fig. 2. The probability of male or female patients not having anti-HBs after becoming HBsAg(+). Numbers in parentheses are number of patients at risk. Males are less likely than females to develop anti-HBs.](image2)

![Fig. 3. Age distribution, by sex, of hemodialysis patients who became HBsAg(+). Numbers in parentheses are the percentages of each sex in that age group. Ages are in years. Each asterisk represents one patient. (Ages of two female and four male patients were not obtained.)](image3)
chronic hepatitis, post-necrotic cirrhosis, and primary hepatocellular carcinoma.

We wish to thank Dr. Baruch S. Blumberg and the members of the Clinical Research Division of The Institute for Cancer Research for their assistance and advice. We also thank the patients and staff of the Delaware Valley Artificial Kidney Clinic in Philadelphia, PA, for their active cooperation with this project. This work was supported by U.S. Public Health Service Grants CA-06551, RR-05539, and CA-06927 from the National Institutes of Health and by an appropriation from the Commonwealth of Pennsylvania.

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