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Delayed Development of Antibody to Hepatitis B Surface Antigen After Symptomatic Infection with Hepatitis B Virus

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During a 2-year period, 38 patients with clinical hepatitis B virus infection were seen at the Public Health Service Alaska Native Hospital in Bethel. This hospital serves an area in southwest Alaska that is hyperendemic for hepatitis B virus. The patients came to the hospital at various times from 15 scattered villages, and 92% were Eskimo. None of the patients had a recent history of hypodermic injection or blood transfusions. Twenty-five patients, all originally positive for hepatitis B surface antigen (HBsAg), were followed for up to 5 years after onset of illness, and 15 were either slow to develop, or never developed, antibody to HBsAg (anti-HBs), although only one patient became a chronic carrier of HBsAg. Six patients had a prolonged "window phase" between the disappearance of HBsAg and the appearance of anti-HBs which lasted for more than 1 year. Three patients had only transient anti-HBs after HBsAg disappeared, and five never developed measurable anti-HBs at all. All patients had antibody to hepatitis B core when both HBsAg and anti-HBs were absent. In contrast to studies in other populations, only 42% had anti-HBs 1 year after onset of illness, 63% had it at 18 months, 70% had it at 2 years, and 80% had it at 5 years. Factors related to ethnicity might account for the differences in the development of anti-HBs after acute symptomatic hepatitis B virus infection seen in Eskimos when compared with whites.

Southwest Alaska has recently been shown to be an area hyperendemic for infection with hepatitis B virus (HBV). The prevalence of HBV infection in Eskimo villages is as high as 73%, and in some villages as many as 23% of the residents are asymptomatic carriers of hepatitis B surface antigen (HBsAg) (3). In adition, a significant number of HBsAg carriers in this region have e antigen (HBeAg) in their serum (9). Environmental sampling studies in these villages imply that HBV infection could be transmitted in various ways; however, hypodermic injection is not one of them (11).

Asymptomatic HBV infection affects many population groups (13), but little is known about the incidence of acute symptomatic hepatitis B in areas where HBV is hyperendemic. We therefore did a prospective study to estimate the incidence of symptomatic hepatitis B in southwest Alaska over a 2-year period. Furthermore, persons with clinical cases of hepatitis B identified during this study period were followed for up to 5 years after the onset of illness to determine the serological response to acute symptomatic infection with HBV.

MATERIALS AND METHODS

Study area. The Bethel Service Unit of the Alaska Area Native Health Service is the sole provider of health care for the 12,000 people who live in southwest Alaska on the delta of the Yukon and Kuskokwim Rivers. The people of this sparsely populated area of 75,000 square miles (ca. 120,000 km^2) reside in 52 villages. Two-thirds of the inhabitants are Eskimo, and the remainder are Athabascan Indians and whites. Each village has at least one community health aide who holds daily clinics and relays medical information by radio to physicians at the Public Health Service Alaska Native Hospital in Bethel. Public health nurses and physicians from the hospital visit the outlying villages at various times throughout the year.

Clinical cases. All patients in the Bethel Service Unit diagnosed as having clinical hepatitis between 1 July 1972 and 30 June 1974 were included in the study. The patients either came to the hospital because of illness, were reported by the community health aide by radio and then sent to the hospital, or were referred by nurses or physicians during field trips to the vil-

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lages. Demographic data and history of blood transfusions, parenteral drug use, alcohol consumption, recent use of isoniazid, and contact with family members with hepatitis during the study period were obtained from patients, community health aides, and a thorough review of hospital records. Local sanitation practices were also reviewed.

A case of hepatitis was defined as the acute onset of icterus and a rise in bilirubin and transaminase levels in a patient who had no history of previous liver disease. A percutaneous liver biopsy was performed on patients in whom the diagnosis of viral hepatitis was uncertain.

Serological follow-up. Of the 38 patients, 25 had serial blood specimens collected for follow-up of HBsAg and antibody to HBsAg (anti-HBs). Any specimens that were initially negative for HBsAg and anti-HBs were retested for HBsAg, anti-HBs, and also antibody to hepatitis B core (anti-HBc), and these specimens were subsequently diluted 1:10 and 1:100 and retested a third time for anti-HBs to rule out a prozone effect. The tests for HBsAg, anti-HBs, and anti-HBc were performed by solid-phase radioimmunoassay with commercially available reagents (AUSRIA II, AUSAB, CORAB, Abbott Laboratories, North Chicago, Ill.) by the Hepatitis Laboratories Division, Bureau of Epidemiology, Centers for Disease Control, Phoenix, Ariz. Specimens on individuals were originally tested for clinical purposes when first collected, but in retesting, all serial specimens from each individual were run in single batches to minimize any possible effect of variation in laboratory procedures on test results.

RESULTS

Clinical cases. During the 2-year study period, 39 cases of clinical hepatitis were diagnosed in the Bethel Service Unit, yielding an annual incidence of clinical disease of 16 per 10,000 population. While they were ill all patients but one were positive for HBsAg, and that patient soon developed anti-HBs. Patients ranged in age from 4 to 62 years. Fifty-six percent were male, and 44% were female. Of the 39 patients, 36 (92%) were Eskimo, two were part Eskimo and part Athabascan Indian, and one was white. The latter was lost to follow-up. At the onset of illness, the mean serum aspartate aminotransferase in these patients was 1,152 IU (range, 182 to 2,900 IU), and the mean total bilirubin level was 8.4 mg/dl (range, 2.5 to 22.4 mg/dl). Four of the patients had liver biopsies performed to confirm the diagnosis; three of the four were known abusers of ethanol, and the other had active renal tuberculosis. All four of these patients had pathological findings consistent with acute viral hepatitis. None of the patients died from this illness.

Epidemiology. One-third of the patients lived in the town of Bethel (population, 2,800), and the others were from 14 isolated villages located in a 50,000-square-mile (ca. 80,000 km^2) area surrounding Bethel. No patient had a history of receiving a blood transfusion within a year before becoming ill, and none gave a history of parenteral drug abuse. Three patients had potential occupational exposure to HBV (two were health aides and one was a dental technician), but none gave a history of needle puncture. Five patients had a history of drinking at least 16 ounces (ca. 480 ml) of whiskey per day. None of the 39 patients was taking isoniazid.

The 39 patients belonged to 34 households. Three patients were from the same household, and three households had two patients each.

Serology. During the acute phase of illness, serum from 38 of the 39 patients was positive for HBsAg. Twenty-five of these patients, all of whom were Alaskan natives, were followed serologically for 12 to 63 months (mean, 34.2 months; median, 31 months) after the onset of illness. The total follow-up for these 25 patients was 855 months or 71.25 patient-years. The average interval between the collections of specimens for serological testing was 8.6 months.

Only one patient became a chronic carrier of HBsAg. The other 24 patients had four other types of distinct serological responses to acute infection. Figure 1 shows the serological responses of a representative patient from each of the four groups. Group A includes 10 patients who had anti-HBs within 1 year after becoming ill or who had anti-HBs on the first follow-up determination. Two of these ten patients had a reasonably short "window phase," lasting 7 to 10 months, between the disappearance of HBsAg and the appearance of anti-HBs.

Group B includes six patients who had a relatively prolonged window phase (14 to 61 months) between the disappearance of HBsAg and the appearance of anti-HBs. During this window phase, serum specimens from the patients in group B were repeatedly negative for HBsAg and anti-HBs but were positive for anti-HBc. Two patients were transiently positive for HBsAg during this prolonged window phase. One of these was negative for HBsAg and anti-HBs at 12 months and 21 months after onset of illness, but then positive for HBsAg and antibody to HBeAg (anti-HBe) 24 months after onset of illness. He again lost HBsAg but at 61 months finally developed anti-HBs for the first time. Another patient in group B was positive for HBsAg and anti-HBs 1 year after onset of illness; 5 months later she had only anti-HBs, and this was still the situation 16 months later.

Group C included five patients followed for up to 61 months (mean, 27 months) who lost HBsAg but did not develop anti-HBs. Their follow-up

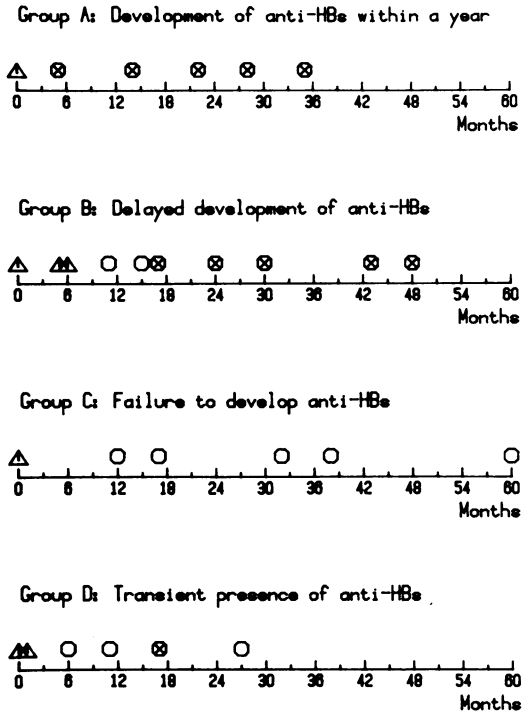

FIG. 1. *Typical patients representing four groups with distinctly different serological responses after acute hepatitis B infection. Symbols: △, HBsAg; ⊗, anti-HBs; ○, anti-HBc only.*

serum specimens were repeatedly positive for anti-HBc. Group D included three patients (mean follow-up, 46 months) who became negative for HBsAg and who were only transiently positive for anti-HBs. At all other times they were negative for both HBsAg and anti-HBs but positive for anti-HBc.

Of the 24 patients who did not become chronic carriers of HBsAg, 15 had either delayed appearance of anti-HBs or did not have anti-HBs at all during the period of follow-up (Fig. 2). Only 42% of this group had anti-HBs within 1 year after clinical illness, and at 18 months 63% had anti-HBs. By 2 years, 71% were found to have anti-HBs, and only an additional 8% developed anti-HBs in the period between 2 and 5 years after clinical illness. Of the 24 patients, 3 had anti-HBs detected only transiently. More females (72.7%) than males (46.2%) had either delayed development of anti-HBs or no anti-HBs during the follow-up period; however, this difference was not statistically significant. There was no relationship between peak levels of serum aspartate aminotransferase at the onset of illness, or whether patients were under or over 30

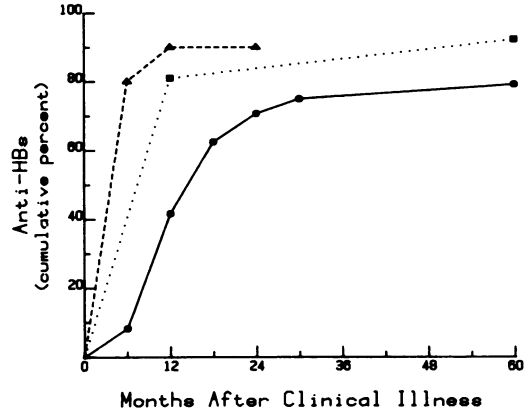

FIG. 2. *Development of anti-HBs after symptomatic hepatitis B infection: comparison of three study groups. Symbols: ▲- - -▲, U.S. volunteer male prisoners (7, 8); ■· · ·■, patients in Los Angeles (6); ●——●, Alaskan natives.*

years of age, and the subsequent development of anti-HBs.

DISCUSSION

The annual incidence of clinical viral hepatitis in the Bethel Service Unit during the 2-year study period was five times higher than reported rates in the United States for the same period (4). All cases had serological evidence of infection with HBV, but no patients gave a history of recent transfusion or self-administered injection. Since illicit use of drugs administered by needle was not known to occur in this isolated area of Alaska before 1974, the absent history of needle use is likely to be reliable. This is, therefore, one of the few published studies that does not include any patients exposed to hypodermic injections (12).

The 39 hepatitis patients diagnosed in this 2-year period came from 34 separate households in 15 villages scattered throughout the region, illustrating that the disease is endemic and widespread. Because 38 of these patients had measurable HBsAg just after the onset of their clinical illness, and the one who did not soon developed anti-HBs, most sporadic cases of hepatitis in southwest Alaska appear to be caused by HBV.

An unexpected result of our study was that most of our patients did not have anti-HBs within the first year after they recovered from illness. In fact, five of our patients never had measurable anti-HBs, three others were only transiently positive for anti-HBs, and six had a prolonged window phase of at least 12 months before anti-HBs appeared. All follow-up speci-

mens from these patients were positive for anti-HBc when they were negative for HBsAg and anti-HBs, indicating that the patients were truly infected with HBV.

The serological findings for our patients are in direct contrast to those found in earlier studies of acute hepatitis B affecting humans and chimpanzees. In studies of volunteer prisoners exposed to material infectious for HBsAg, over 80% of those who had acute symptomatic hepatitis B had measurable anti-HBs within 1 year after onset of illness (2, 5). In another study of 12 mentally retarded children who were exposed to infectious HBV and had acute hepatitis B (7), 9 (75%) had measurable anti-HBs within a year after exposure. In a third study of 26 patients who, like our patients, were not parenteral drug users and had an observed episode of acute hepatitis B, 21 (81%) had measurable anti-HBs within 1 year after illness, and all but two (92%) had measurable anti-HBs when restudied 5 to 9 years later (12). In another study, all chimpanzees that were infected with HBV and did not become chronic carriers had measurable anti-HBs after HBsAg disappeared; the longest window phase between the disappearance of HBsAg and the appearance of anti-HBs was 22 weeks (1). Unfortunately, two additional large long-term studies of acute symptomatic HBV infection measured only HBsAg in follow-up serum specimens to determine what proportion of the subjects became chronic carriers (10, 12). Thus, in those studies reported so far in which both HBsAg and anti-HBs were measured, at least 80% of patients with acute symptomatic hepatitis B who did not become chronic carriers of HBsAg had measurable anti-HBs within 1 year of onset of illness, whereas in our study it took more than 5 years for the same proportion of patients to have measurable anti-HBs.

It is difficult to explain these findings. All specimens were tested twice at different times, and the second time all specimens were tested as a batch. There are several possible explanations. First, some of these patients may have had levels of HBsAg or anti-HBs too low to be detected with radioimmunoassay. In fact, five of our patients were transiently positive for HBsAg or anti-HBs, two of them during their long window phase. Second, other patients may have had low levels of circulating HBsAg and anti-HBs complexes that could not be detected. One of our patients did have transient evidence of the presence of both HBsAg and anti-HBs. A third possibility is that anti-HBs was present for a short time, but did not persist. This phenomenon has been reported elsewhere to occur in only about 10% of symptomatic patients (2, 6). In our study, once anti-HBs appeared, it persisted in all but 4 of 19 patients. A fourth possibility is that some patients may have had too low a level of anti-HBs to be detected after acute infection and may have been reinfected later, since HBV is hyperendemic in this area. This situation might result in a booster effect and the later appearance of anti-HBs. Although this phenomenon could possibly explain the long window phase that six of our patients had, there is no evidence that this actually occurred.

It is possible that ethnic differences in response to acute HBV infection may exist. A prolonged window phase has been shown to occur only rarely in other U.S. population groups (8, 12). All earlier long-term studies of acute symptomatic hepatitis B involved U.S. populations and did not report data by race. Since 92% of our patients are Eskimo, it is possible that ethnic differences may account for the different patterns of antibody development seen in this study. The prevalence of asymptomatic carriers in our population, as well as certain other population groups, such as Asians and West Africans (4), is high. Poor immunological recognition of HBV by particular ethnic groups could result in either no anti-HBs response, an anti-HBs response too low to measure with radioimmunoassay, or a delayed response. Since our study involves the only long-term follow-up of patients with acute symptomatic infection with HBV belonging to an ethnic group with known high prevalence of HBsAg carriers, other studies are needed to further delineate anti-HBs response to acute HBV infection in members of similar groups, such as Asians and Africans. This information is badly needed because of its implications for HBV vaccination campaigns directed at high-risk members of such ethnic groups.

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