EPIDEMIC OF HEPATITIS E IN A MILITARY UNIT IN ABBOTTABAD, PAKISTAN

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Abstract. An outbreak of hepatitis caused by hepatitis E virus (HEV) in Abbottabad, Pakistan was traced to fecal contamination of a water system. Of 109 men hospitalized with hepatitis, 104 (95%) had serologic evidence of acute hepatitis E (IgM antibody to HEV [anti-HEV]), three (3%) probably had acute hepatitis E (high titers of IgG anti-HEV without IgM), and two had acute hepatitis A. Among a subset of 44 men with acute hepatitis E from whom three serum specimens were obtained over a four-month period, the anti-HEV IgG geometric mean titers (GMTs) decreased from 1,519 during the outbreak to 657 at four months. The IgM anti-HEV was detected in 40 (91%) of 44 sera obtained at admission (GMT = 533 during acute disease), but in only six (14%) four months later. The prevalence of anti-HEV in this population before the outbreak was estimated to be 30%. The presence of IgG anti-HEV appeared to protect against clinical hepatitis or development of serologic evidence of new infection with HEV. This is the second major epidemic of hepatitis E in the Pakistani military confirmed by an anti-HEV enzyme-linked immunosorbent assay (ELISA). Evidence that pre-existing antibody as measured by this ELISA protects against disease is important for assessment of vaccine development.

INTRODUCTION

Hepatitis E virus (HEV) is recognized as a common cause of epidemic and sporadic viral hepatitis, especially in Asia1,2 and Africa,3-6 with epidemic7 and sporadic cases8 also reported from Mexico. In addition to civilian cases, hepatitis E outbreaks have been documented in military populations in Chad,9 Djibouti,10 Nepal,11 Ethiopia,12 and among Bangladeshi soldiers serving with the United Nations Forces in Haiti.13 French and Italian soldiers, but apparently not American or Belgian Forces serving in Somalia,14 have also been infected. Military15 and paramilitary16 forces in India have also experienced outbreaks of non-A, non-B enterically transmitted hepatitis. Epidemic hepatitis E has been reported in Pakistan in a military unit in Sargodha17-19 and in the capital city of Islamabad.20

In the present report, we describe an outbreak of non-A, non-B hepatitis that occurred in a military academic community in Abbottabad, Pakistan. This was apparently caused by an isolate of HEV that is genetically distinct from the HEV strain that caused the Sargodha outbreak. Genetic analysis of a fecal isolate of HEV from an outbreak in Sargodha indicated that it was closely related to isolates from China across the Hindu Kush mountains from Pakistan. In contrast, an isolate from the present outbreak that occurred in 1988 in Abbottabad was genetically related to south Asian isolates from India, Burma, and Nepal.21 Therefore, at least two genetically distinguishable isolates of HEV have caused outbreaks of hepatitis E in the Pakistani military.

The Abbottabad epidemic provided an opportunity to study the serologic response to HEV infection in a large number of individuals over time using serum specimens from patients with hepatitis. In addition, we prospectively studied persons exposed to the same food and water as patients (contacts), as well as persons who were presumably not exposed (controls).

The main purposes of this study were to describe the epidemiologic and clinical features of HEV infection with this genetically distinct isolate, and to describe the pattern of antibody to HEV (anti-HEV) in serum over time using a sensitive serologic technique. The secondary purposes were to assess prospectively the prevalence of anti-HEV, to determine the number of sub-clinical cases, to monitor for secondary spread of infection, and to determine possible protection provided by pre-existing antibody. Understanding the spectrum of epidemiologic and clinical features of hepatitis E caused by different strains will be important for optimal use of vaccines for hepatitis E, which are being developed.

MATERIALS AND METHODS

Investigation of the outbreak. In August 1988, the Pakistan-United States Laboratory for Seroepidemiology (PULSE) in Rawalpindi, Pakistan was notified of cases of hepatitis admitted to a military hospital in Abbottabad, Pakistan. Abbottabad is located in the foothills of the Himalayan Mountains 116 km northwest of Rawalpindi and Islamabad and 217 km northeast of Peshawar in the Northwest Frontier Province (Figure 1). An investigative team from the PULSE in Rawalpindi joined members from the hospital in Abbottabad during an initial investigation from August 22 to 24, 1988. Through August 23, 68 persons were hospitalized with a diagnosis of hepatitis (Figure 2), as manifested by anorexia, nausea, occasional vomiting, malaise, dark urine, and icterus. Bile salts were present in the urine, and most had elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). There was no history of mass immunization or use of medications that might have caused hepatitis. Most of the cases were part of the Headquarters Company of the Pakistan Military Academy in Abbottabad. All patients were living in unit housing. None of the men of the unit living off the base was ill.

Based on previous evaluations of enterically transmitted hepatitis in Pakistan,18,19 a questionnaire and patient data collection form were completed for each patient and serum samples were collected. Serologic evaluations for hepatitis A and B were conducted on these initial specimens at the PULSE using enzyme immunoassay test kits (Abbott Laboratories, North Chicago, IL). Of the first 65 patients studied, none had IgM antibody to hepatitis B core antigen (anti-HBc)
or IgM antibody to hepatitis A virus, but 22 had anti-HBc and two had hepatitis B surface antigen.

In addition to hospitalized patients, two cohorts were studied prospectively. During the initial visit, sera were obtained from 41 housing contacts, defined as persons who were not ill but lived in the same housing complex and who obtained drinking water from the same source as the cases. For controls, sera were obtained from 57 persons who were not ill, but who lived in different housing areas (Junior Commissioned Officers and men living with their families) with a different water supply.

**Environmental assessment.** Water samples were obtained from the main water supply (spring), the reservoir distribution tanks, water line to the barracks, messing facility for general duty personnel, and food. These were processed microbiologically for coliform bacteria at the PULSE.

The team returned to Abbottabad on August 29, 1988 and collected additional samples from patients admitted between August 24 and 28. A technician from the PULSE remained at the hospital to collect specimens from new patients.

On a third visit on September 21, follow-up sera were collected from 63 patients admitted in August, 30 of the contacts of patients, and 30 controls. During a fourth visit on December 6, 1988, sera were collected, based on availability, from 70 patients, eight contacts, and one control. All serum specimens were stored at the PULSE at −70°F.

To ship specimens to the United States, specimens were packed under dry ice at the PULSE, transported on a military medical flight, and immediately transported to Uniformed Services University where they were held at −70°F until analysis. No freeze-thaw cycles occurred during transport.

**ELISA for anti-HEV.** An ELISA was used to detect IgG and IgM anti-HEV in serum. Briefly, a baculovirus insect cell system was used to express a 55-kD antigen from open reading frame 2 (ORF-2) of the HEV (strain Sar 55) genome originally isolated during the Sargodha outbreak. This antigen was used to capture anti-HEV in a solid phase ELISA. Sera were tested at dilutions of 1:100, 1:1000, and 1:10,000

**Statistical analysis.** Reciprocal geometric mean titers (GMTs) of anti-HEV were calculated. For this calculation,
specimens in which antibody was not detected were arbitrarily assigned a value of one and values $\geq 10,000$ were considered 10,000. Chi-square and Fisher’s exact test were used for comparing outcomes as appropriate.

Human experimentation guidelines. Human experimentation guidelines of the U.S. Department of Health and Human Services, the Uniformed Services University of the Health Sciences, and the Army Medical College were followed in conducting this outbreak investigation.

RESULTS

Epidemiology. Between August 4 and September 19, 1988, 109 adult males with clinical hepatitis were admitted to the hospital (Figure 2). Their average age was 28 years (range = 18–59 years). Clinical findings are shown in Table 1. Dark urine, scleral icterus, and anorexia were each noted in more than 90% of the cases. Biochemical testing revealed bile salts in the urine (in all 78 tested), and elevated levels of ALT, AST, alkaline phosphatase, and total bilirubin.

All cases occurred among a single group of men who lived in a housing area on the base for unmarried or unaccompanied men. There were approximately 800 men living in this area. Cases of hepatitis had not been reported from this group of men in the previous year, and cases were not noted during the epidemic period among men who lived in a different housing area on the base. These findings suggested a common-source outbreak.

Investigation of possible sources of food or water contamination revealed that sanitation in the unit cooking houses, dining halls, barracks, and latrines was satisfactory. There was no overcrowding in the barracks. The water line to the cook houses where food was prepared for the men of the ordinary services (general infantry) was excavated and found to be defective and leaking. Since water flow had been intermittent, investigators believed that during periods of negative pressure in the water pipes, the water had been contaminated by sewage from nearby septic tanks. Examination of water in the holding tank did not reveal coliform bacteria. In contrast, water obtained beyond the area of water pipe leakage and closer to the living/cooking quarters of the affected group had a coliform count $> 180$ colonies/100 mL.

Corrective and preventive measures included repair of the broken pipe, superchlorination of the water supply, washing of fruits and vegetables with superchlorinated water, strict handwashing by those preparing and eating food, and surveillance for additional cases. Following these corrective measures, there were no additional cases reported by the hospital after September 20, 1988.

Findings in patients. There were 109 persons admitted to the hospital with acute jaundice (Figure 2). These included four patients initially classified as contacts, but who were hospitalized on August 24 (two patients) and September 10 and 18, respectively. Of the original 105 patients, IgG anti-HEV was detected in 103 (98%), and IgM anti-HEV was detected in 97 (92%) in the first serum sample (Table 2). Of the eight patients in whom IgM anti-HEV was not detected in the initial serum sample, two had acute hepatitis A (one with acute hepatitis B concurrently). Of the remaining six patients, IgM anti-HEV was subsequently detected in three patients. All six had IgG anti-HEV (five with titers $\geq 1:1,000$ and one at 1:100). In addition to the original 105 patients, all four contacts who were later admitted had IgG and IgM anti-HEV in sera collected on admission. Therefore, of 109 hospitalized persons, a serologic diagnosis of acute hepatitis E (IgM anti-HEV) was made in 104 (95%), three probably had hepatitis E (high titer IgG anti-HEV), and two had acute hepatitis A. The crude attack rate for hepatitis E was therefore 13% (107 of 800).

Serum samples were collected at all three time points (August, September, and December) from 44 patients admitted in August (Figure 3). Among these 44 patients, IgM anti-HEV was highest in the initial serum sample, with a GMT of 533. The mean IgM titer decreased to 152 an average of 29 days later, at which time IgM was detected in 36 (82%) of the 44 patients. In December, an average of 104 days after the initial serum, IgM was detected in only six (14%) of the 44 patients, all at the lowest dilution tested (1:100) yielding a GMT of 2. IgG anti-HEV was detected in all specimens at each time

| Table 1 |

Clinical signs and symptoms reported by 109 patients admitted with hepatitis between August 4 and September 19, 1988 in Pakistan*

<table>
<thead>
<tr>
<th>Finding</th>
<th>No. of patients reporting</th>
<th>Percent with finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark urine</td>
<td>104</td>
<td>95</td>
</tr>
<tr>
<td>Scleral icterus</td>
<td>103</td>
<td>94</td>
</tr>
<tr>
<td>Anorexia</td>
<td>103</td>
<td>94</td>
</tr>
<tr>
<td>Nausea</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Fever</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>Light-colored stools</td>
<td>49</td>
<td>45</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Pruritis</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

* Includes four persons originally designated as contacts but who were hospitalized with hepatitis E.

| Table 2 |

Prevalence of IgM and IgG antibodies to hepatitis E virus in serum specimens collected from cases, contacts, and controls at Abbottabad, Pakistan during August, September, and December, 1988 according to original classification

<table>
<thead>
<tr>
<th></th>
<th>August 4–September 19</th>
<th>September 21</th>
<th>December 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>IgG</td>
<td>IgM*</td>
<td>IgG</td>
</tr>
<tr>
<td>All cases</td>
<td>97/105 (92%)</td>
<td>103/105 (98%)</td>
<td>51/63 (81%)</td>
</tr>
<tr>
<td>Contacts</td>
<td>5/41 (12%)</td>
<td>12/41 (29%)</td>
<td>7/30 (23%)</td>
</tr>
<tr>
<td>Controls</td>
<td>0/57 (12%)</td>
<td>18/57 (32%)</td>
<td>2/30 (7%)</td>
</tr>
</tbody>
</table>

* Represents paired sera from 63 patients admitted August 4–30.
† Persons living in the same housing area. Includes four persons originally designated as contacts but who were admitted to the hospital with acute jaundice on August 24 (2 cases), September 10, and 14, respectively.
The GMTs of IgG anti-HEV decreased from 1,519 in August to 1,299 in September and to 657 in December. Thus, titers of IgG anti-HEV were highest in the first sera and decreased by more than 50% during the next four months.

Potentially exposed persons from the same housing area (contacts). Forty-one serum samples were initially obtained from contacts. Five were positive for IgM anti-HEV; two of these were almost immediately hospitalized with clinical hepatitis E and three had subclinical infections. Of the remaining contacts, 28 were available for prospective assessment of subclinical infections, secondary cases, and the protective effect of pre-existing IgG anti-HEV (Table 3).

Twenty-one of them were seronegative and seven (25%) had IgG anti-HEV at the time of their first bleeding. Among the 21 seronegative individuals, 10 seroconverted; two of them had clinical hepatitis E and were hospitalized in September and the remaining eight had subclinical infections. Thus, the subclinical to clinical infection ratio was 4:1.

There was no convincing evidence for secondary transmission (person-to-person spread). The last of the hospitalizations among the contacts was on September 18, approximately 26 days after the water supply was repaired. In addition, the seroconversions that occurred between August 24 and September 21 in the eight subclinically infected individuals were within one incubation period of exposure. Therefore, the onset of clinical and subclinical infections in this group was well within the usually accepted incubation period for HEV of up to 40 days.

Seven of the 28 prospectively followed contacts had IgG anti-HEV initially. None of these seven seropositive individuals had evidence of a new HEV infection (absence of IgM anti-HEV or of increased titers of IgG anti-HEV). Compared with the 10 infections among the 21 seronegative contacts, these IgG positive individuals appeared to be protected from new HEV infections ($P = 0.03$, by Fisher’s two-tailed exact test).

**Controls.** Fifty-seven controls that were in the same unit but who lived in a different area were also evaluated to obtain a background rate of exposure to hepatitis E and to monitor for additional cases. None had IgM anti-HEV at the time of the initial bleeding. IgG anti-HEV was present in 18 (32%) and 15 of them had anti-HEV titers of only 1:100, the lowest dilution tested. These low titers suggested old infections. Thirty of the controls were studied prospectively. Twenty were seronegative at the time of the initial bleeding. Two of these had newly detectable IgM and IgG anti-HEV in the subsequent bleeding (Tables 2 and 3). Neither was hospitalized. Therefore, two (10%) of 20 seronegative controls demonstrated serologic evidence of recent HEV infection without clinical illness.

Ten of the 30 prospectively followed controls were positive for IgG anti-HEV (but negative for IgM anti-HEV) at the time of the initial bleeding. None of these developed IgM anti-HEV or an increase in the IgG anti-HEV titer, suggesting that they were not reinfected with HEV. Therefore, two of 20 controls without pre-existing anti-HEV were infected with HEV, whereas none of the 10 individuals with pre-existing antibody developed serologic evidence of infection ($P = 0.79$). If data from both controls and contacts are combined (Table 3), protection afforded by pre-existing anti-HEV is further suggested: 20 (29%) of 41 compared with zero of 17 were infected ($P = 0.01$).

**DISCUSSION**

This study documents that HEV was the etiologic agent of this point-source epidemic of hepatitis among young military men in Pakistan. Anti-HEV was detected in nearly all cases at the time of admission. The study demonstrates the pattern of IgM and IgG anti-HEV over a period of months. This study also demonstrates that the rate of sub-clinical infection is high, the background prevalence of anti-HEV appears to be high in this population, secondary spread of infection was...

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**TABLE 3**

Clinical and serologic outcomes of contacts and controls studied at the time of the outbreak and at least one month later according to presence of antibody to hepatitis E virus (anti-HEV) in the initial specimen

<table>
<thead>
<tr>
<th></th>
<th>IgG anti-HEV initially absent</th>
<th>IgG anti-HEV Initially Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contacts</td>
<td>Controls</td>
<td>Total</td>
</tr>
<tr>
<td>Total with new infection</td>
<td>10†</td>
<td>2</td>
</tr>
<tr>
<td>No evidence of infection</td>
<td>11</td>
<td>18</td>
</tr>
</tbody>
</table>

* Two contacts who had IgG and IgM anti-HEV at the time of enrollment were hospitalized within two days of collection of the initial sera sample and are not included.

† Defined as new IgM alone, new IgG alone, or new IgG and IgM anti-HEV.

‡ Includes two persons who were hospitalized with hepatitis in September and eight subclinical infections.
minimal in this outbreak, and antibody to HEV appears to protect against subsequent clinical illness.

This is the second well-documented outbreak of hepatitis E in military personnel in Pakistan. The first occurred at a military high school in Sargodha and was also thought to result from the contamination of a water supply.\textsuperscript{17,18} Other outbreaks of suspected hepatitis E have occurred in Pakistani military populations in Rawalpindi, Mardan, and Quetta\textsuperscript{24} (Figure 1). At least 50\% of cases of sporadic hepatitis admitted to military hospitals in Rawalpindi, Pakistan, are non-A, non-B hepatitis (presumably hepatitis E).\textsuperscript{25–28} In 1993–1994, a large outbreak of hepatitis E occurred in Islamabad, the capital of Pakistan, as a result of contamination from a malfunctioning water treatment plant. Almost 4,000 cases were reported\textsuperscript{29}.

ELISA testing for anti-HEV confirmed the cause of this outbreak as HEV. This assay, which uses the ORF2 of HEV, was judged to be highly sensitive (96\%) and specific (98\%) when compared with other assays in a test of a coded panel of sera.\textsuperscript{30} Sera from this outbreak have been evaluated by a non-commercial Genelabs ORF2 antigen assay and found to have a high level of reactivity.\textsuperscript{31} Direct comparison of these two ORF2-based tests using another set of sera from Saudi Arabia yielded a concordance of 96.3\% and 92.2\% for detection of IgG and IgM anti-HEV, respectively.\textsuperscript{31}

In this investigation, sera collected at all three time points were available from 44 patients, permitting a more accurate description of the kinetics of anti-HEV. IgG anti-HEV was detected in all cases with hepatitis at the time of admission. IgM was detected in 91\% at admission, but in 95\% using paired sera. IgM anti-HEV decreased within weeks and could be detected in only 14\% of patients four months after admission, while IgG anti-HEV was present in all patients four months after the onset of the outbreak. These data are consistent with findings in the Sargodha outbreak, in which IgG antibody was detected in all patients studied 20 months after illness.\textsuperscript{17} IgG anti-HEV was observed more than four years after acute infection of a U.S. traveler to Pakistan\textsuperscript{32} and as long as 14 years after clinical hepatitis E.\textsuperscript{33}

Clinical signs and symptoms caused by this HEV strain were similar to those caused by a different strain in the Sargodha outbreak.\textsuperscript{18} One notable difference was that fever was reported by 49\% of patients in the Abbottabad outbreak compared with 29\% of those hospitalized at Sargodha. There were no deaths in either outbreak. In general, signs and symptoms of acute hepatitis are similar among cases caused by hepatitis viruses A, B, and E.

Little is known about subclinical infection with hepatitis E. A significant observation in this study was the detection of subclinical infection among contacts and controls. Among contacts, the subclinical to clinical ratio was 4:1. This ratio is higher than those reported from an outbreak of hepatitis E in Nepalese soldiers in which subclinical infection occurred 2.8 times as often as clinical hepatitis\textsuperscript{11} or when compared with subclinical rates which were twice as high as disease rates in military and police personnel in Nepal.\textsuperscript{34} This may have resulted from the small number (10) of persons observed or that the diagnostic assay used in the Nepalese studies was less sensitive than the assay used in the present study.

The prevalence of antibody to HEV in Pakistan is unknown. The prevalence of IgG anti-HEV (without IgM) in contacts of cases in the Sargodha outbreak was 50\%,\textsuperscript{17} while in the present outbreak in Abbottabad, the prevalence was 22\% (8 of 37) in contacts and 32\% (18 of 57) in controls. The combined prevalence in contacts and controls (28\%) is similar to that observed for IgG (without IgM) in Nepalese soldiers in an outbreak situation (30\%).\textsuperscript{13} Cross-sectional studies in Nepal and India indicate that the prevalence of anti-HEV increases with age.\textsuperscript{34,35} In both studies, the prevalence increased from 16\% in young adolescents to 31\% in those more than 40 years old. Therefore, although the numbers of persons studied is relatively small, the prevalence of IgG anti-HEV observed in contacts and controls in the present study in Pakistan is similar to that observed in Nepal and India.

The crude attack rate of 13\% (107 of 800) in the affected housing area may be an underestimate. Assuming that the background prevalence of antibody to hepatitis E was 32\% as suggested from studies of the control population, then only 554 men would have been susceptible and the attack rate among susceptible men may have been as high as 19\%.

Evidence for secondary (person to person) spread within the barracks was minimal. The four cases among the contacts occurred within the same time frame as other cases, and no additional cases were noted between September and December. The outbreak can be explained by a common source exposure. Secondary spread of hepatitis E appears to be much less common than secondary spread of hepatitis A.\textsuperscript{36} The source of infection of the two persons among the control group who developed subclinical cases of hepatitis E is unknown, but may reflect background rates of infection in this population. It is possible that these persons were exposed to water at the barracks where the outbreak occurred or to other contaminated water elsewhere.

Pre-existing anti-HEV as measured by this assay appears to correlate with protection against hepatitis E. During another epidemic in Pakistan, men who had naturally acquired anti-HEV also were protected. Additional data from the present study suggest that naturally acquired anti-HEV protected contacts from infection, as well as from disease. Studies in non-human primates indicate that anti-HEV, whether due to prior infection or passive or active immunization against HEV, successfully protects against challenge with HEV.\textsuperscript{22,26,37–39} These findings are especially important for the development and deployment of hepatitis E vaccines.

The current study extends our knowledge of the clinical findings in HEV infection, the pattern of immunologic anti-HEV response, the incidence of subclinical infection, and the background prevalence of anti-HEV in this military population. It confirms the lack of secondary spread of HEV infection, and the protective nature of antibody. Hepatitis E remains an important cause of morbidity among military personnel, tourists, refugees, and civilian populations in endemic areas. A vaccine to protect against hepatitis E would be an important adjunct to prevention of this enteric disease.

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