

THE ROLE OF HEPATITIS E VIRUS INFECTION AMONG PATIENTS WITH ACUTE VIRAL HEPATITIS IN SOUTHERN SAUDI ARABIA

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We investigated the etiology of acute sporadic viral hepatitis in southern Saudi Arabia in a series of 132 patients admitted with acute viral hepatitis. Of these cases, 108 (81.8%) were due to acute hepatitis A virus infection, of which 11 (8.3%) patients had been previously exposed to hepatitis E virus, and another 10 (7.6%) were chronic carriers of hepatitis B virus. Three cases (2.3%) were acute hepatitis B virus infection. The overall prevalence of hepatitis E IgG antibodies was found to be 9.1%. The remaining 21 (15.9%) patients were tested for hepatitis E IgM, EBV-VCA IgM and hepatitis C IgG antibodies by sensitive enzyme immunoassays. In none of them could hepatitis E IgM, EBV-VCA IgM or hepatitis C IgG antibodies be demonstrated, and these patients were thus considered as acute non-A, non-B hepatitis. Acute hepatitis C virus infection, however, could not be ruled out from this group. We therefore concluded that the majority of clinically apparent viral hepatitis cases were due to HAV, while HBV accounted for a small proportion of the cases. Clinically apparent HEV infection does not appear to be common in the population studied, since even those with serologic evidence of previous exposure to HEV did not recall a history suggestive of acute viral hepatitis. *Ann Saudi Med* 1997;17(1):32-34.

Viral hepatitis is an important health problem in the southern part of Saudi Arabia. The prevalence of hepatitis B (HBV) is about 10%,¹ with delta (HDV) virus occurring both as co- and superinfections. The prevalence of hepatitis C (HCV) is 1.4% among healthy blood donors² and earlier studies have shown that hepatitis A (HAV) virus infection accounted for 43% of acute viral hepatitis cases requiring hospitalization.³ Following the introduction of HBV vaccination and its integration in the immunization program in October 1989 in Saudi Arabia,⁴ together with the expected introduction of the recently licensed HAV vaccine,⁵ it is hoped that the magnitude of these infections will eventually decline. However, other hepatitis viruses such as hepatitis E (HEV) and HCV may continue to pose a problem. The recent development of enzyme immunoassays for the detection of markers of acute (HEV) virus infection¹² have prompted us to study the prevalence of HEV infection among patients admitted with acute viral hepatitis and also to cast some light on the prevalence of HEV infection in this region.

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TABLE 1. Characteristics of the 132 patients with acute hepatitis.

Age group	Sex		Nationality		Total
	Male	Female	Saudi	Others*	
3-10	50	32	76	6	82
11-20	15	6	19	2	21
21-30	14	2	3	13	16
31-40	5	0	1	4	5
>40	7	1	4	4	8
Total	91	41	103	29	132

Material and Methods

This study enrolled all 132 cases clinically diagnosed as acute viral hepatitis (classified in Table 1) admitted to Lasan Infectious Disease Hospital, the single hospital of its kind in the region. All patients (or their relatives) were specifically questioned regarding a past history of jaundice, surgical operations, blood transfusions, medications, intravenous drug abuse, alcohol ingestion or recent travel abroad.

On admission, 3 mL to 6 mL of sera were obtained from all patients, aliquotted in 200 μ L volumes and were either tested immediately, or kept frozen in vials at -20° C and tested at a later date. Clinical specimens were initially tested for hepatitis A virus-specific IgM, HBsAg, and anti-HBc IgM utilizing commercially available enzyme-linked immunosorbent assays (ELISA) kits HAVAB-M, enzyme monoclonal HBsAg and corezyme-M, respectively (Abbott

TABLE 2. Classification of patients with relation to infection, age and biochemical data.

	Age	ALT	AST	BIL-T	BIL-D	No. total (%)
HAV IgM	8±4*	171±40	99±38	7.0±3.0	4±2.2	87/132 (65.9)
HAV IgM, HEV IgG	11±5	127±77	85±27	4.5±2.7	3±1.7	11/132 (8.3)
HAV IgM, HBsAg, HBcIgG	26±10	172±51	133±40	11±5.0	7±3.0	10/132 (7.6)
HBsAg, Hbc IgM	25±5	200±14	117±35	12±5.0	7±2.4	3/132 (2.3)
Negative for all markers**	22±14	187±34	86±25	5.4±3.0	3.8±2.0	21/132 (15.9)

*Mean±ISD; **classified as "non-A, non-B" cases (an Indian in this group was IgG-HEV-positive).

TABLE 3. Distribution of anti-HEV IgG among the different age groups of 132 patients with acute hepatitis.

Age groups (years)	No. positives/total (%)
3-5	2/132 (1/5)
6-10	3/132 (2.3)
>10	7/132 (5.3)
Total	12/132 (9.1)

Laboratories Diagnostic Division, Chicago, Ill.). Specimens were additionally tested for IgG HCV antibodies by a second-generation ELISA kit, detecting antibodies reacting with the C-100, c33c and c22-3 regions of HCV genome (Sanofi Diagnostics Pasteur, Marnes La Coquette, France) and also for IgG HEV antibodies by a recombinant antigen ELISA (Abbott). Furthermore, non-reactive sera were also tested in an indirect ELISA (*in vitro* diagnostika GmbH, Mainz-Kastel, Germany) for Epstein-Barr viral capsid antigen (VCA)-specific IgM. The 21 specimens proven nonreactive in all of the above IgM immunoassays were retested for HEV IgM (and IgG) in an ELISA utilizing recombinant antigens as follows: initially, all sera were tested at 1:20 and 1:100 dilutions with the SG3 epitope in ORF2 of the Burmese strain of HEV, and were additionally tested with a pool of 4-2M (ORF3, Mexico), 4-2B (ORF3, Burma) and 3-2M (ORF2, Mexico), as previously described by Yarbough et al.¹² In all commercially available assays, test procedures and evaluations of the results were performed according to the manufacturers' instructions. Biochemical levels of liver enzymes alanine (ALT) and aspartate (AST) aminotransferases and bilirubin levels (total and indirect, Bil-t, Bil-d, respectively) were obtained from patients' records. Relevant data was entered in a computer and statistical analysis was done with GraphPad Prism software (GraphPad Software Inc., San Diego, CA, USA).

Results

The majority of patients (108, 81.8%) diagnosed with acute viral hepatitis have had an acute HAV infection: of these (Table 2), 10 Saudis and an Indian (7.6%), with a mean age of 11 years, were previously exposed to HEV (Table 3) and another 10 patients (7.6%, mean age 26 years) were also chronic carriers of HBV. As expected, except for the chronic carriers of HBV, most of the patients were below the age of 12. Two Saudis and another Indian (2.3%, mean age 25 years) were acute cases of HBV infection. The remaining 21 patients (15.9%, mean age 22 years) were negative for HAV IgM, HEV IgM, HBsAg and anti-HBc IgM, HCV IgG, EB VCA-IgM and except for an Indian, all were HEV-IgG negative. This group of patients (eight Saudis, 6.1%; six Egyptians, 4.5%; three Pakistanis, 3.0%; two Indians, 1.5%; and a Filipino, 0.8%) were considered as cases of acute non-A, non-B hepatitis. One of the six Egyptians was a female and the rest were male, and none of them had an identifiable risk factor for viral hepatitis. Statistical analysis did not show any significant difference in the biochemical markers (Table 2) among the different groups of these patients.

Discussion

Hepatitis E virus (HEV) has recently been recognized as the major etiological agent of enterically transmitted non-A, non-B (ET-NANB) hepatitis. It is now well established that HEV was responsible for major outbreaks of ET-NANB in India, Pakistan, Bangladesh, Nepal, Burma, Algeria, Somalia, Sudan, Ivory Coast, and Mexico.⁶⁻¹¹ The introduction of new assays for the detection of HEV^{12,13} and HCV^{14,15} have further expanded the scope of our knowledge regarding the viral causes of hepatitis. The results of the present study have clearly demonstrated that HEV infection does not seem to play a significant role in the etiology of acute sporadic viral hepatitis in the indigenous population in southern Saudi Arabia, despite the fact that a large sector of expatriates from endemic areas work in this region. None of the patients tested had HEV-specific IgM antibodies. These data seem to confirm those recently reported from Spain¹⁶ and France.¹⁷ In the Spanish study, not one of 341 patients with acute sporadic hepatitis had evidence of acute HEV infection, while in the French study, only one case was documented with a recent history of travel to Pakistan. It is well established from an epidemiological study that the highest attack rate among cases with clinically overt hepatitis E infection is observed in those between 20 and 40 years of age, although several sporadic cases of acute hepatitis E were recently identified among children (two months to 15 years) in Egypt and Sudan.^{13,18-20} In our study, acute HAV infection accounted for all cases with

acute viral hepatitis in the age group below 20 years. However, past HEV infection with the presence of IgG HEV seropositive cases was documented as early as three years of age (Table 3). It appears that the majority of sporadic HEV infections were either subclinical or nonspecific, occurring as early as three years and gradually increasing with age (Table 3), since in none of the 12 (9.1%) IgG-HEV seropositive cases (two Indians and 10 Saudis) was a past history of jaundice elucidated. These findings seem to support the hypothesis of Lok and Soldevila-Pico²¹ that HEV infection may be endemic in many areas and not necessarily imported. Indeed, the majority (81.8%) of the acute viral hepatitis cases were due to HAV (with or without previous exposure to HEV or HBV, Table 2). This poses a major health problem in terms of its prevention and control. With the advent of the newly introduced HAV vaccine, together with the established public health measures in the Kingdom, it is hoped that HAV infection will eventually be controlled. The results presented in this study, however, may not reflect the actual exposure to HEV in the region, since the population sample was relatively small (and biased by being patients), and furthermore, the majority of these patients were children (Table 1). Nevertheless, surveys from other regions of Saudi Arabia have shown a similar prevalence of HEV infection (range 8.4% to 14.9%).²²

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