ACUTE VIRAL HEPATITIS IN SOUTH-EASTERN OF IRAN: A SEROLOGICAL ANALYSIS OF 263 CASES

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Abstract- There is no report on the etiology of acute viral hepatitis in Sistan and Baluchestan province, southeast of Iran. We performed this study to compare the clinical, biochemical and demographic properties of acute viral hepatitis (AVH) in this province. Demographic and clinical data were collected from 263 patients with AVH. They were tested for HBsAg, IgM anti-HAV, IgM anti-HBc, IgM anti-HDV, or IgM anti-HCV. Numbers of patients with hepatitis A, B, C, D and non A-D were: 188 (75.5%), 47 (17.9%), 6 (2.3%), 5(1.9%) and 17(6.6%), while mean ages were 6.1, 20.6, 20.2, 26.2 and 18.7 years, respectively. Hepatitis A patients presented with lower initial serum levels of bilirubin, ALT and AST, but higher alkaline phosphatase, and they were more likely to have anorexia, vomiting, fever, chills, abdominal pain and prodromal symptoms. Nearly all cases of AVH in children were due to Hepatitis A, whereas hepatitis B, C and D generally occurred in adults. There were some differences in clinical and laboratory findings regarding to the etiology.

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INTRODUCTION

Acute viral hepatitis (AVH) is an important cause of morbidity and mortality worldwide. However, its incidence varies widely as it is low in developed countries but high in parts of South America, Africa, and Asia including the Middle East. Common forms of AVH are currently hepatitis A, B, C, D and E. The relative importance of these five agents differs dramatically with the geographical region. For example, in the United States, hepatitis A, B and C account for 97% of all cases of AVH (1). In some regions such as Senegal, Tunisia, and Ethiopia about 20 percent of all cases of AVH are hepatitis C (2). In Northern parts of India, China and Pakistan, hepatitis C is a rare cause of non A non B hepatitis, whereas hepatitis E has a high prevalence (3, 4). In view of dissimilar prognosis of different types of hepatitis and elementary differences between measures for epidemiological investigations and control programs, determination of etiology of AVH is crucially important for the patients, their families, and community (5).

There is no report on the etiology of AVH in Sistan and Baluchestan province, southeast of Iran. Therefore, we decided to determine the relative importance of recognized etiologic agents of AVH; and to compare the clinical, biochemical and demographic factors associated with each type of AVH in Zahedan, the capital city of the province.

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The situation in Sistan and Baluchestan province is special. Because it is located near the border between Iran and Pakistan and Afghanistan, there are large amounts of Afghan refugees and the province comprises the highest rate of hepatitis infection throughout the country. Therefore the results of this study provide useful information for health policy makers and physicians.

MATERIALS AND METHODS

Blood samples as well as demographic and clinical data were collected from 263 consecutive patients with sporadic AVH who were seen at Zahedan Hepatitis Clinics and Bu-Ali and Ali-Asghar Hospitals. These two hospitals are the only ones that have infectious diseases department. Since patients in whom AVH is suspected are almost always referred to one of these centers for diagnosis and management, our subjects represented most of the clinically evident cases of AVH in Zahedan during 2000 to 2002. The study was approved by Ethics Committee of Zahedan University of Medical Sciences and written informed consent was obtained from all subjects.

The infectious diseases specialists at the hospitals and the hepatitis clinic made the clinical diagnosis of AVH. The diagnosis was based upon an illness with <1 month of duration with symptoms compatible with acute hepatitis, an initial serum level of alanine aminotransferase (ALT) of more than 5 times the upper limit of normal, and exclusion of the other potential nonviral causes of hepatocellular injury and ruling alcoholic hepatitis, chronic liver disease, anoxic hepatitis, drug hepatitis and systemic diseases such as malaria, typhoid and brucellosis out by conventional clinical and laboratory studies.

For each suspected case of sporadic AVH presenting to the hepatitis clinic and the hospitals an initial blood sample was taken and tested for serum bilirubin and serum liver enzyme levels. On the basis of clinical and biochemical findings, the infectious diseases specialists made the clinical diagnosis of AVH as described above.

Following physical examination, all 263 patients with AVH completed a detailed questionnaire in a 10 to 15-minute interview and provided a blood sample, which was sent to the Zahedan Blood Transfusion Organization laboratory. The questionnaire included demographic information, data on risk factors for hepatitis during the previous 6 months, and patients' symptoms and signs.

Each serological testing was performed without awareness of the results of other serologic tests. The sera were tested by EIA for IgM anti-HAV, hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and for IgM antibody to hepatitis B core antigen (anti-HBc). All HBs-Ag-positive sera, with or without IgM anti-HBc, were tested by EIA for antibodies to HDV (anti-HDV).

Acute hepatitis A was diagnosed if the serum sample was positive for IgM anti-HAV. Acute hepatitis B was diagnosed if the serum sample was positive for IgM anti-HBc. Patients with HBsAg and anti-HDV who were lacking IgM anti-HBc were considered as having hepatitis D superinfection. Hepatitis C was diagnosed if the serum was positive for anti-HCV or HCV RNA at initial visit or 3 months later. AVH type non A-D was defined by the absence of serological markers of recent infection with HAV, HBV, HCV and HDV. Hepatitis E was not investigated because pertinent diagnostic kits were not available.

Frequency distributions were compared using chi-square testing. The *t* Student test was used for the comparison of mean values in two independent groups and one-way analysis of variance (ANOVA) for comparison of mean values of numerical variables across the different etiologic types of AVH. F test was used for the evaluation of significance. All values were expressed as mean ± SD. A *P* value of <0.05 was considered as significant.

RESULTS

Of 263 cases of AVH, 93.5% were attributed to one of the four investigated hepatitis viruses (Table 1). HAV was the most frequent etiologic agent, accounting for 188 cases (71.5%, CI 95% = 65.9-77.1). Next was HBV, accounting for 47 cases (17.9%, CI 95% = 13.2-22.6); HCV was the etiologic agent in only 6 cases (2.3%, CI 95% = 0.5-4.1) and HDV in only 5 cases (1.9%, CI 95% = 0.2-3.6).

Table 1. Characteristics of patients with different types of hepatitis*

Variable	Type of hepatitis A (n=188)	B (n=47)	C (n=6)	D (n=5)	Non A-D (n=17)
Male sex	97 (52)	30 (64)	4 (67)	3 (60)	5 (19)
Age (year)†	6.1	20.6	20.2	26.2	18.7
0-4 years	86 (47)	2 (5)	0 (0)	0 (0)	3 (18)
5-14 years	88 (48)	15 (32)	2 (33)	0 (0)	3 (18)
15-65 years	11 (6)	30 (64)	4 (67)	5 (100)	11 (65)
Outpatient	176 (94)	33 (77)	5 (83)	3 (60)	15 (88)
ALT (mg/dl)†	825	1049	926	1317	916
AST (mg/dl)†	808	1219	1128	1665	1267
Total bilirubin (mg/dl)†	6.1	10.7	8.5	25	13.9
ALK Ph†	663	332	493	288	389
Duration of illness before presentation (days) †	7.3	11.2	14	13.4	10.9

Abbreviations: ALT, alanin amino transferase; AST, aspartate amino teransferase; ALK Ph, Alkaline phosphatase.
* Data are given as number (percent) unless specified otherwise.
† Data are given as Mean.

All of the HDV cases were considered as superinfection in HBV carriers. The exact cause of acute hepatitis was not diagnosed in 17 patients (6.5%) in whom the disease might be due to hepatitis E, or other viral hepatitis, autoimmune hepatitis or other causes.

The demographic and biochemical parameters across the etiology of AVH are shown in Table 1. Of all patients, 139 (52.9%) were male. The relative frequency of Hepatitis A in both genders had no difference, however, the relative frequency of Hepatitis B, C and D in male was more than female (Table 1). They were aged in a range of 1 to 65 years with a mean of 10.1 years. Hepatitis A occurred most frequently in young children and hepatitis B, C and D occurred generally in young adults. Mean ages of patients affected by hepatitis A, B, C, D and non A-D were 6.1 (CI 95%, 5.4-6.9), 20.6 (CI 95%, 17.5-23.7), 20.2 (CI 95%, 5.7-34.7), 26.2 (CI 95%, 16.2-36.2) and 18.7 (CI 95%, 10.9-26.4), respectively. Hepatitis A patients presented to the hospitals or clinic earlier (P = 0.01), and had lower initial serum levels of bilirubin, ALT and AST, but not alkaline phosphatase (ALP). The outpatient cases comprise 94.1% of hepatitis A and 66.7% of hepatitis B patients. All but one hepatitis C cases were among the outpatients. Hepatitis D cases consisted of 3 outpatients and 2 in-patients.

The signs and symptoms of hepatitis A vs. parenteral transmitted hepatitis cases (B, C and D) are shown in Table 2. The ones with parenteral transmitted hepatitis were more likely to have excoriation, however patients with hepatitis A were more likely to have anorexia, vomiting, fever, chill, abdominal pain and prodromal symptoms (coryza, cough, throat pain). Since jaundice and dark urine were components of the case definition, almost all patients with AVH had these signs.

Table 2. Signs and symptoms of patients*

Signs and Symptoms	Hepatitis A	PTH	Odds ratio (CI 95%)
Hepatomegaly	17 (9)	9 (15)	0.5 (0.2-1.4)
Splenomegaly	10 (6)	5 (8)	0.6 (0.2-2.1)
Anorexia	180 (96)	41 (71)	9.3 (3.5-25.5)
Nausea	124 (66)	39 (70)	0.8 (0.4-1.7)
Vomiting	95 (51)	17 (30)	2.3 (1.2-4.7)
Dark Urine	182 (98)	55 (98)	0.8 (0.6-1.5)
Rigor	34 (18.1)	3 (5.2)	4 (1.1-17.2)
RUQ pain	47 (27)	16 (28)	0.9 (0.5-1.9)
Coryza	40 (24)	3 (6)	5.4 (1.5-23)
Cough	35 (21)	3 (6)	4.6 (1.3-19.5)
Throat pain	12 (7)	1 (2)	4.1 (0.5-87.1)
Diarrhea	33 (20)	7 (13)	1.6 (0.6-4.3)
Constipation	30 (18)	16 (29)	0.6 (0.3-1.2)
Excoriation	28 (17)	19 (35)	0.4 (0.2-0.8)
Abdominal pain	131 (79)	33 (60)	2.6 (1.3-5.2)
Fever	149 (79)	34 (61)	2.5 (1.2-4.9)

Abbreviation: Parenteral transmitted hepatitis.
*Data are given as number (percent).

DISCUSSION

It was found that the most common cause of acute viral hepatitis in Zahedan was hepatitis A (75.5%). It was followed by hepatitis B (14.7%). Hepatitis A was the most common cause of AVH in children, but hepatitis B was the most common cause of AVH in adults. This study was one the first studies that provided an analysis on the etiology of AVH in Iran; where all types of AVH is medically important.

In developing countries infection with hepatitis A takes place in the first years of life and 90% of children acquire this infection before 10 (6). A study in Sistan & Baluchestan province showed 89% of children younger than 5-year-old were affected by hepatitis A infection (7). On the other hand, it is known that hepatitis A is often asymptomatic in young children. In spite of this fact, we found that it was the main cause of clinical AVH among this age group in the city of Zahedan. However, in adults, hepatitis A was a rare cause of acute hepatitis. This seems to be due to the high incidence of hepatitis A infection among children and this early acquisition of infection prevents getting the infection later in life. It is similar to the results of studies conducted in the Middle East and developing countries (8-13).

Although hepatitis B infection is prevalent in most developing countries, its prevalence differs in some countries. About 20% of population in Iran has been infected by HBV (14). A study in Zahedan showed a ratio of 34% for hepatitis B infection (15). Therefore, hepatitis B infection and, consequently, acute hepatitis B is prevalent in Zahedan; however it is the cause of only 14.3% of acute cases of viral hepatitis. This low ratio can be due to a high share of acute hepatitis A in one hand and universal vaccination of neonates against hepatitis B since 1993, on the other hand. Incidence of HBV infection decreased in US in recent two decades following HBV vaccination (1, 16). In the same way it is predicted that HBV infection would continuously decrease in Iran.

Acute hepatitis D superinfection was diagnosed in 9 cases. HDV is endemic in the Mediterranean area and the Middle East and has been reported to cause acute and chronic liver disease in those regions (9). In Iran, 3-14% of chronic hepatitis B carriers are also carriers for chronic hepatitis D (14). In the present study, 1.8% of acute viral hepatitis cases were due to hepatitis D, and in fact 11% of all cases of acute hepatitis B were along with hepatitis D. Similarly, in Saudi Arabia 10% of acute hepatitis B cases had hepatitis D infection too (17).

HCV seems to be a rare but important cause of AVH in the region, although, it is difficult to differentiate acute from chronic form of infection. We know that HCV infection is very low at present in general population of Iran. Studies conducted in Fars and Sistan & Baluchestan provinces showed that only 0.1-0.2 percent of population were infected with HCV virus (18, 19).

The etiology of 17 cases (6.7%) of AVH remained undiagnosed, probably some of them were due to hepatitis E. Nevertheless, we can conclude that hepatitis E is not as prevalent as hepatitis A and B in this region. There is no report of seroepidemiology of hepatitis E in Iran.

Contrary to some previous reports (5, 9), in our study clinical and laboratory factors were useful in predicting the etiology of AVH in individual cases. Those with hepatitis A had lower serum levels of bilirubin, ALT and AST. A Spanish study showed that fatigue, anorexia, fever, chills and lymphadenopathy were more common in hepatitis A (20). Bilirubin levels were higher in patients with hepatitis B (10.3) and C (9.7) compared with hepatitis A (6.7). Alanine aminotransferase (ALT) levels where higher in patients with hepatitis B. However it may be an age related issue as in the present study patients with hepatitis A were significantly younger than patients with other types of hepatitis and it is known that severity of AVH has an inverse correlation with age (21). Cholestatic hepatitis is a clinical presentation of acute hepatitis A especially in children and this can explain the higher serum level of ALP in hepatitis A patients (22).

There are limited records on etiology of AVH in Iran. Similar studies are required to achieve evident data on this issue at the other parts of the country.

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Conflict of interests

The authors declare that they have no competing interests.

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