Original Article

Proportion of hepatitis A and E among chidren with acute viral hepatitis with special reference to differences in their clinico-biochemical parameters: A hospital based study

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Received - 15 October 2019 Initial Review - 01 November 2019 Accepted - 21 November 2019

ABSTRACT

Background: Hepatitis is a major health problem in both developing and developed countries, with various infective and non-infective causes. **Aim:** This study aims to estimate the proportion of hepatitis A and E as a causative agent in children presenting with acute hepatitis and to study their clinical and biochemical parameters. **Materials and Methods:** The present study was conducted on all children attending or admitted with clinical features of acute hepatitis defined as hepatomegaly, fever >38°C, malaise, dark urine, and/or jaundice. All children included were clinically examined and relevant investigations were sent. All the data were entered in a structured pro forma and statistical analysis was done. **Results:** A total of 254 patients were studied. Hepatitis A virus (HAV) was the most common with 95.08% of cases and occurred in the age group of ≤5 years. Hepatitis E virus (HEV) was more common in ≥10 years age group and was observed in 13.11% of cases. Common prodromal symptoms in hepatitis patients were fever, anorexia, vomiting, and abdominal pain, observed in 82.5%, 32.5%, 55.5%, and 50.5% of cases, respectively, with no significant difference between HAV and HEV. In liver biochemistry, there was no significant difference in serum bilirubin, serum glutamic oxaloacetic transaminase, and serum glutamate pyruvate transaminase values between HAV and HEV. **Conclusion:** There are no significant differences in both enterically-transmitted hepatitis viruses and the only way to differentiate between them is by serological tests.

Key words: *Bilirubin, Hepatitis, Hepatitis A virus, Hepatitis E virus, Serum glutamate pyruvate transaminase, Serum glutamic oxaloacetic transaminase*

Hepatitis is a major health problem in both developing and developed countries and viral hepatitis is the most common cause of hepatitis in children. Among the hepatotropic viruses, hepatitis A virus (HAV) and hepatitis E virus (HEV) are enterically transmitted and hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus are parenterally transmitted [1]. In India, HAV and HEV infections have assumed endemic proportions. HAV mainly affects children, whereas HEV is more common among young adults [2]. In developing countries, HAV constitutes approximately two-third of sporadic acute viral hepatitis (AVH) in children [3]. Greater awareness and availability of laboratory diagnosis has resulted in identifying HEV as an important cause of sporadic AVH even in children (up to 59%) [4]. In India and other developing countries, HAB is also common (3–34%) among children with sporadic AVH [5].

In preschoolers, HAV is the most frequent cause of hepatitis [6]. It was reported that HAV infection in children usually exhibits mild nonspecific symptoms and low case fatality in comparison to adults [7]. In general, HAE resembles HAV, having similar routes of transmission and clinical picture. However, it has a longer incubation period and affects older children and adults and is responsible for significant number of cases of sporadic hepatitis and is an important cause of acute liver failure (ALF) [8].

Large annual epidemics are attributed to HEV, and studies suggest that it is etiologically responsible for 10–95% of admitted cases of hepatitis across South Asia [9]. Due to the use of HAV vaccine, HEV is now emerging as an important cause of AVH [10]. The aim of this study was to estimate the proportion of hepatitis A and E as a causative agent in children presenting with acute hepatitis and to study their clinical and biochemical parameters.

MATERIALS AND METHODS

This observational hospital-based study was conducted in the department of pediatrics medicine of a tertiary center of Western India, a large teaching hospital in Jaipur, the capital city of Rajasthan, India. Children attending to or admitted in the hospital with clinical features of acute hepatitis defined as hepatomegaly, fever >38°C, malaise, dark urine, and/or jaundice were enrolled after taking written informed consent from parents/guardian.

Sample size was calculated at 80% study power and alpha error 0.05 assuming the occurrence of hepatitis A and E separately as 15% according to the results obtained in seed article.

The inclusion criteria applied in case selection were onset of symptoms <12 weeks, age >6 months–<18 years, total serum bilirubin >2 mg/dl, and aspartate aminotransferase/alanine aminotransferase >200 IU/L. Exclusion criteria were patients with liver disease who were undergoing treatment with a hepatotoxic drug and patient with acute hepatitis due to metabolic errors and autoimmunity.

All the details were recorded using a uniform medical questionnaire and details about significant past and family history were taken. Vitals were recorded and temperature was measured by digital thermometer. Systemic examination was carried out particularly of abdomen and central nervous system examination. All subjects were investigated for complete blood count, serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), prothrombin time, and international normalized ratio (INR), and viral marker serology. All the data were entered into structured pro forma and statistical analysis was done.

Human serum or plasma collected was used as sample. After blood collection, serum was separated from the clot as soon as possible. If the assay was performed within 48 h of sample collection, the samples were kept at 2–8°C; otherwise, deep-frozen (−20°C or below) storage was done. The presence or absence of immunoglobulin M (IgM) anti-HAV was determined by comparing the absorbance value of unknown samples to that of the cutoff value. Complete blood count was done by autoanalyzer. Liver biochemistry – SGOT and SGPT were done by kit of ERBA Diagnostics Mannheim GmbH (Germany). PT/INR was done by NEOPLASTINE CI PLUS.

DiaSorin S.p.A. (Italy) ETI-HA-IGMK-PLUS No 142 was used for estimating IgM antibodies of hepatitis A. DIA.PRO (Diagnostic Bioprobes Srl, Italy) ELISA kit was used for the determination of IgM antibodies to HEV in human serum and plasma. HEPACARD (Diagnostic Enterprises, India) was used for the one-step rapid visual qualitative detection of hepatitis B surface antigen (HBsAg) in human serum/plasma. HCV TRI-DOT (Diagnostic Enterprises, India) kit was used for rapid visual qualitative detection of antibodies to hepatitis C in human serum/plasma.

All the data were entered into Master Chart prepared in Microsoft Excel 2007 and statistical analysis was done using Microsoft Excel, Chi-square test and unpaired t-test using statistics calculator Stat Pac version 3.

RESULTS

Out of the 254 patients enrolled in the study, 200 were viral marker positive. HAV was the most common virus implicated in AVH causing 66.92% of cases followed by HBV 6.69% and HEV 5.90% (Table 1).

There was no statistically significant difference in the sex-wise distribution in HAV and HEV infection. The highest proportion of cases of hepatitis A was in the age group of ≤5 years with 95.08% of the total marker positive patients, whereas the highest proportion of cases of hepatitis E was seen in the age group of ≥10 years with 13.11% ($p<0.05$) (Table 2).

Prodromal phase symptoms of AVH were compared between enterically-transmitted hepatitis and statistical analysis was done.

As shown in the Table 3, most common prodromal symptoms in hepatitis patients were fever, anorexia, vomiting, and abdominal pain with 82.5%, 32.5%, 55.5%, and 50.5%, respectively. It was seen that in prodromal phase of hepatitis, the non-specific symptoms were not significantly different ($p>0.05$). There was no significant difference among jaundice, bleeding, and encephalopathy manifestation in hepatitis A and E patients ($p>0.05$).

Liver biochemistry in relation to serum bilirubin, SGOT, SGPT, and coagulopathy showed no significant difference between HAV and HEV. Similarly, there was no significant difference in significant coagulopathy and etiological agent ($p>0.05$) as per the Table 4. Out of the 63 cases of ALF, 42 cases (66.67%) were due to hepatitis A and 1 case (1.5%) was due to hepatitis E.

Table 1: Distribution of total cases of acute hepatitis in the study population

Acute hepatitis Etiology	Number of cases	Percentage
HAV	170	66.92
HEV	15	5.90
HBV	17	6.69
Coinfection HAV and HEV	1	0.39
Coinfection HAV and HBV	1	0.39
None	54	21.25
Total	254*	100

*Since two patients have coinfection total number of cases comes out to be 254. HAV: Hepatitis A virus, HEV: Hepatitis E virus, HBV: Hepatitis B virus

Table 2: Age distribution of the study population

Age group	Total (n=200)	Hepatitis A, (%)	Hepatitis E, (%)	p-value
≤5 years	61	58 (95.08)	1 (1.63)	0.03
5–10 years	78	67 (85.89)	6 (9.8)	
≥10 years	61	45 (73.77)	8 (13.11)	
Total	200	170	15	

Table 3: Clinical presentation and complication profile

Clinical presentation/ complication	Hepatitis A virus (n=170), (%)	Hepatitis E virus (n=15), (%)	p-value
Fever	140 (82.35)	12 (80)	0.90
Vomiting	92 (54.11)	8 (53.34)	0.83
Abdominal pain	83 (48.82)	9 (60)	0.57
Anorexia	59 (34.70)	4 (26.67)	0.73
Jaundice	159 (93.52)	13 (86.67)	0.63
Bleeding	21 (12.35)	0 (0)	0.30
Encephalopathy	22 (12.94)	1 (6.67)	0.76

Table 4: Comparison of liver biochemistry in patients of hepatitis A and E

Liver biochemistry	Hepatitis A (n,%)	Hepatitis E (n,%)	p value
Serum bilirubin, mean±SD	6.91±4.85 mg/dl	6.14±4.90	0.589
Serum glutamic oxaloacetic transaminase (IU/L), mean±SD	1146.65±1075.9	798.1±697.7	1.230
Serum glutamate pyruvate transaminase (IU/L), mean±SD	1139.9±893.5	849.2±706.5	1.226
INR <1.5	113 (66.47)	13 (86.67)	0.25
INR ≥1.5–2	21 (12.35)	1 (6.67)	
INR ≥2	37 (21.76)	1 (6.67)	

SD: Standard deviation, INR: International normalized ratio

DISCUSSION

Out of 254 cases taken in this study, 170 cases were positive for hepatitis A IgM serology (66.92%) and HEV IgM was positive in 15 cases (5.90%). Furthermore, 54 patients (21.25%) had none of the markers positive in their serological study. A study done by Jang *et al*. found the existence of IgM anti-HAV in 77% of the cases and that of IgM anti-HEV in 2% of cases [11]. These results were in accordance to the present study. Earlier studies aimed at determining the cause of AVH showed HAV positivity 18.7–52%, HEV 31–52%, and HBsAg positivity around 11.5%. At present, hepatitis E is the most common cause of AVH in adults [12,13]. This might be due to the epidemiological shift due to introduction of hepatitis A vaccination in Western world. Moreover, with improvement in sanitary and hygiene practices, the occurrence of hepatitis A has now shifted from early childhood to adolescence.

A number of studies have been conducted in India regarding the causative agent of AVH [14-16].

In the present study, the study population was divided into three age groups of ≤5 years, 5–10 years, and ≥10 years. The maximum cases of AVH and HAV were in the age group of 5–10 years. However, the highest number of HEV cases was in the age group of ≥10 years. It was observed that as the age increased proportion of HAV decreased.

These results were similar to findings observed by Escobedo-Meléndez *et al.,* wherein the mean age was 7.2±3.8 years [17]. They showed a significant increase in anti-HAV IgM prevalence in the school-aged group and reduction in prevalence of adolescents. The mean age in the study by Kumar *et al*. was 7±3 years [16]. In a study by Malathi *et al*., age distribution was as follows: <6 years – 47.9%, 6–10 years – 44.1%, and >10 years – 7.9%; however, they included children up to 12 years of age [15]. In a similar study by Radhakrishnan *et al*., HAV positivity was 52.7% in children <12 years and 9.2% in children >12 years and for HEV, it was 5.5% and 18.5%, respectively, which was in accordance with the present study [14]. In a study by Singh *et al*., viral marker positive cases were 61.1% in children <6 years and 38.9% in children >6 years [18]. Data have shown that HEV infection occurs more often in older children and adults while HAV occurs mostly in children under 12 years of age.

In our study, the most common clinical presentation was jaundice (93%) followed by fever (82.5%), vomiting (55.5%), abdominal pain (50.5%), and hepatomegaly (48.5%). Escobedo-Meléndez *et al*. found jaundice in 96% and hepatomegaly in 98% of cases [17]. The variation in symptoms can be due to geographic variation and development status of country. Singh *et al*. observed fever in 92% of cases, jaundice in 100%, and hepatomegaly in 75.9% of cases.

ALF was found in 63 patients (24.80%) of the total study population. Out of these, 42 (66.7%) were due to HAV and 1 case (1.5%) due to HEV. Escobedo-Meléndez *et al*. found 3% incidence of ALF [17]. In a study of Jang *et al*., the fulminant hepatitis rate was 0.5% which comprised cases of HAV only [11]. This finding is in accordance to the epidemiology of hepatitis A where it is the leading cause of ALF in developing countries. In a study done by Singh *et al.,* fulminant hepatitis was documented in 8 of 54 cases (14.8%) [18]. In a study by Malathi *et al*., 13% of children developed hepatic failure and 13% of children died [15].

In our study, hepatitis A and E coinfection was reported in 1 (0.39%) patient. This was comparatively lower than that observed by Joon *et al*. [19]. Coinfection with HEV and HAV did not affect the prognosis as these cases improved after symptomatic treatment. Acute hepatitis A is usually improved by conservative management, but it was found that coinfection of HAV and HEV may lead to severe forms of disease such as hepatic encephalopathy [19].

The limitations of the present study include that it was a hospital-based study, which may not be representative of the community. Furthermore, it was a single-institution research and further studies would be needed to test whether the same findings are applicable in other areas too.

CONCLUSION

There is no significant difference in enterically-transmitted hepatitis viruses. Both cause same symptoms with similar examination findings and biochemical profile. Only way to differentiate them is by serological tests. Coinfection of hepatitis viruses was also detected in some cases.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Semwal P, Gandhi A, Gupta RK, Vajpayee S. Proportion of hepatitis A and E among chidren with acute viral hepatitis with special reference to differences in their clinico-biochemical parameters: A hospital based study. Indian J Child Health 2019; December 13 [Epub ahead of print].