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Original Article

Clinico-biochemical profile and etiology of acute viral hepatitis in hospitalized children: A study from Eastern India

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ABSTRACT

Background: Acute viral hepatitis (AVH) in children continues to be a major public health problem in India. **Objective:** To identify the etiology, and to assess the clinical and biochemical profile, complications and outcome of AVH in children. **Materials and Methods**: A total of 76 children with the clinical diagnosis of AVH were included in this record based retrospective study from January 2014 to August 2016. Data on clinical characteristics, laboratory parameters, immediate outcome, and treatment received were obtained, and analysis was performed. **Results**: Specific etiological agents were identified in 84.2% children. Out of these, 93.7% were due to a single virus, whereas 6.3% were due to mixed infection. Hepatitis A virus (HAV) was found to be the sole infecting agent in 75% children. Hepatitis B virus (HBV) and hepatitis E virus (HEV) were found in 12.5% and 6.2% children, respectively. Mixed infection was seen in the form of HAV and HEV in 3.1%, and HAV and HBV in 3.1%. The mean age of children with hepatitis A was 8.29±2.74 years, with 70.8% boys and 29.2% girls. Common clinical features were jaundice (95.8%), loss of appetite (95.8%), tender hepatomegaly (68.8%), fever (50%), vomiting (50%), pain abdomen (33.3%), splenomegaly (31.2%), itching (27.1%), bleeding (2.1%), and seizure (2.1%). Acute liver failure was seen in 4.1% and 2% of admitted children died. The mean age of presentation of AVH due to HBV and HEV were 10.7±2.6 years and 10±2.2 years, respectively. Clinical features were similar without any complications or mortality. Significant elevations in hepatic enzymes were seen in mixed infection due to HAV and HEV ($p<0.05$). **Conclusion:** HAV is the primary cause of morbidity and mortality due to AVH in this region. HBV and HEV infection may present with similar clinical features, and serological testing must be done to identify the cause.

Key words: *Children, Hepatitis, Hepatitis A, Hepatitis B, Hepatitis E, Viral hepatitis*

Acute viral hepatitis (AVH) is a primary disease of liver with systemic involvement, mainly caused by five hepatotropic viruses; namely A, B, C, D, and E. It is still a major public health problem of developing countries such as India, despite improving socioeconomic condition, sanitation, and health awareness [1]. The clinical spectrum of AVH ranges from entirely subclinical and inapparent infection to rapidly progressing and fulminant hepatic failure [2]. Hepatitis A (HAV) and E (HEV) viruses are feco-orally transmitted and self-limiting, whereas hepatitis B (HBV), C (HCV) and D (HDV) are transmitted parenterally and may progress to chronic hepatitis.

India is hyper-endemic for hepatitis A and E [3]. HAV is the most common cause of AVH in children, whereas HEV is predominant in adults [4]. Because of the improvement in living standard, the pattern of AVH due to HAV is changing from an asymptomatic or mild infection to an increased incidence of symptomatic or severe disease [5]. HAV is also the most common cause of fulminant hepatitis in children in India and worldwide [6].

HEV has been associated with the large scale of epidemics and outbreaks in various parts of India. It is related to high attack rate and mortality in pregnant women [7]. Though it is a major disease of adults, it can affect children with a similar picture of hepatitis. It is an unlikely cause of fulminant hepatitis in children [8].

In India, HBV infection is of intermediate endemicity, with nearly 4% of the population being chronic carriers [9]. The most cases of acute hepatitis due to HBV are subclinical and less than 1% of symptomatic diseases are fulminant. Young children rarely develop acute clinical disease, but many of those infected before the age of seven become chronic carriers [7]. HCV is an infrequent cause of acute icteric hepatitis [10], but causes most of post-transfusion hepatitis [11]. HDV infection is found in fewer than 10% of patients with acute or chronic HBV infection [12].

Owing to paucity of data on the incidence and etiology of AVH in Indian children, this study was undertaken. The objective of the study was to identify the etiology, and to assess the clinical and biochemical profile, complications and outcome of AVH in children.

MATERIALS AND METHODS

This was a retrospective record based study conducted at a tertiary care teaching hospital of Eastern India. The data from January 2014 to August 2016 were analyzed in a period of 1-month. All the case records of children up to 15 years of age admitted to the hospital with a diagnosis of "AVH" or "viral hepatitis" or "hepatitis" were retrieved from the medical records department. All the children with acute onset of jaundice suggestive of acute hepatitis or having elevated serum transaminase level more than 2 times normal and with at least one positive serological viral marker (immunoglobulin M [IgM] HAV, IgM HEV, hepatitis B surface antigen [HBsAg], and anti-HCV) were included in the study. Children <1 year of age, having chronic liver disease or metabolic disease, biliary obstruction and records with incomplete data were excluded from the study. HBsAg positive but IgM-anti HBc negative children and anti-HCV positive, but HCV RNA negative children were also excluded from the study.

Acute hepatitis was defined as acute illness with discrete onset of symptoms (e.g., nausea, anorexia, fever, malaise, or abdominal pain) with rise of total serum bilirubin (≥2 mg/dl) or elevation of serum alanine aminotransferase (ALT; ≥twice the upper limit of normal) at any point in the course of the disease in the absence of underlying chronic liver disease [13]. Fulminant hepatitis or acute liver failure (ALF) was defined as the presence of biochemical evidence of acute liver injury (<8 weeks duration); no evidence of chronic liver disease; and hepatic based coagulopathy defined as a prothrombin time (PT) >15 s or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or a PT>20 sec or INR >2 regardless of the presence of clinical hepatic encephalopathy [14].

AVH A was diagnosed by the presence of Anti-HAV IgM in the serum. Titer estimation was performed by fully automated bidirectionally interfaced chemiluminescent immunoassay method using HAV Ab-IgM Reagent kit. Values ≥1.2 were considered as positive. Diagnosis of acute hepatitis B was based on the presence of IgM antibody against hepatitis B core antigen (IgM anti-HBc) with or without HBsAg. Acute hepatitis E and hepatitis C were diagnosed by the presence of IgM antibody against HEV (anti-HEV IgM) and anti- HCV antibody, respectively.

Statistical analysis was performed using SPSS software version 20. Univariate and bivariate frequency tables were generated based on categorical data. Association between parameters was studied using chi-square test at appropriate level of significance. Association was considered to be statistically significant at $p<0.05$.

RESULTS

A total of 76 cases with clinical diagnosis of AVH were admitted during the study period of 3-year. 12 cases were excluded as per the criteria (no serological marker in 8 cases, only HBsAg positive in 2 cases and incomplete records in 2 cases). So for the final analysis 64 case records were considered.

In this study, we found hepatitis A in 48 (75%), hepatitis B in 8 (12.5%) and hepatitis E in 4 (6.25%) children. Mixed infection was seen in 4 (6.25%) cases. Two (3.1%) had concurrent infection with hepatitis A and E, whereas the other two (3.1%) had hepatitis A and B. Age distribution of children with AVH is depicted in Table 1.

AVH due to HAV was seen to be more common in boys (70.8%) as compared to girls (29.2%). Age of the patients ranged from 4 to 14 years. Mean age of presentation was 8.29±2.74 years. Maximum number of cases (20.8%) was admitted in the month of August (Fig. 1). The most common symptoms at presentation were jaundice and loss of appetite (95.8%). Other symptoms were fever (50%), vomiting (50%), pain abdomen (33.3%), itching (27.1%), bleeding from mucosal site (2.1%), and seizure (2.1%). Tender hepatomegaly was seen in 68.8% cases, whereas splenomegaly was seen in 31.2% cases. Interloop ascites and pleural effusion on ultrasonography were seen in 10.4 % and 4.2% cases, respectively. The mean duration of hospital stay was 7.42±3.1 days. 47 (98%) children had serum bilirubin levels <10 mg/dl. Serum aspartate aminotransferase (AST) and ALT levels were significantly high (>1,000 U/L) in 6 (12.5%) and 10 (20.8%) children, respectively. ALF was seen in 2 (4.1%) children and one of them (2%) died.

AVH due to HBV and HEV as the sole cause were more commonly seen in boys (75%). The mean ages of presentation were 10.7 ± 2.6 years (range 7-15 years) and 10 ± 2.2 years (range 7-12 years), respectively. The symptoms and signs are illustrated in Table 2. All of them had clinical jaundice at admission. There were no complications or mortality due to HBV and HEV. Tables 3 and 4 show the hematological and biochemical parameters as observed in the three groups of viral hepatitis. We did not find any child affected with HCV or HDV.

Table 1: Age distribution of children with AVH

Age (years)	Hepatitis				
	A (48)	B (8)	E (4)	A+E (2)	A+B (2)
<5	6	0	0	0	0
5-10	30	3	2	2	1
>10	12	5	2	0	1

AVH: Acute viral hepatitis

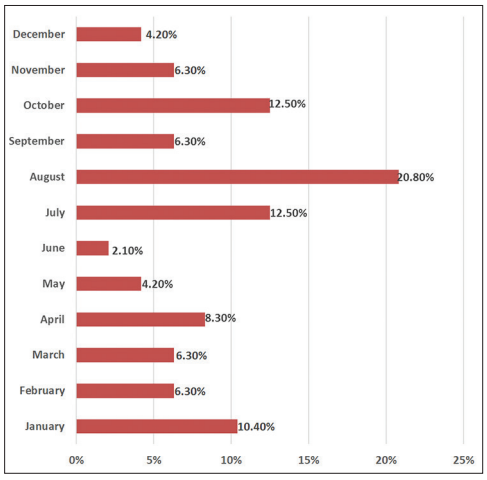

Figure 1: Month wise distribution of children with hepatitis A

Table 2: Clinical and ultrasonographic findings in children with AVH

Symptoms	Hepatitis		
	A	B	E
Jaundice	46 (95.8)	8 (100)	4 (100)
Loss of apetite	46 (95.8)	8 (100)	4 (100)
Fever	24 (50)	5 (62.5)	4 (100)
Vomiting	24 (50)	3 (37.5)	3 (75)
Pain abdomen	16 (33.3)	3 (37.5)	2 (50)
Bleeding	1 (2.1)	0	0
Seizure	1 (2.1)	0	0
Hepatomegaly	33 (68.8)	5 (62.5)	4 (100)
Splenomegaly	15 (31.2)	2 (25)	0
Itching	13 (27.1)	5 (62.5)	1 (25)
Ascitis	5 (10.4)	0	1 (25)
Pleural effusion	2 (4.2)	0	0

AVH: Acute viral hepatitis

Table 3: Hematological parameters in children with AVH

Parameters	Hepatitis		
	A	B	E
Hb (g%)	10.78±1.6	11.11±1.4	12.84±1.03
TLC ($\times 10^3$/cmm)	8.01±2.4	9.07±1.7	7.57±1.2
PCV (%)	34.75±5.2	36.83±4.7	39.78±3.1
MCV (fl)	76.09±10.7	76.69±6.6	88.43±5.7
MCH (pg)	23.44±3.8	23.63±2.0	28.56±1.8
MCHC (%)	30.72±1.09	30.79±1.1	32.3±0.3
Platlet ($\times 10^4$/cmm)	282.38±103.3	309.0±82.7	157.86±135.8

AVH: Acute viral hepatitis, Hb: Hemoglobin, TLC: Total leukocyte count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration

Table 4: Biochemical parameters in children with AVH at presentation

Parameters	HEP		
	A (n=48)	B (n=8)	E (n=4)
Total serum bilirubin (mg/dl)			
Normal	1 (2.1)	0	0
<5	29 (60.4)	1 (12.5)	4 (100)
5-10	17 (35.4)	5 (62.5)	0
>10	1 (2.1)	2 (25)	0
AST (u/l)			
Normal	2 (4.2)	0	0
<500	34 (70.8)	2 (25)	0
500-1000	6 (12.5)	3 (37.5)	1 (25)
>1000	6 (12.5)	3 (37.5)	3 (75)
ALT (u/l)			
Normal	1 (2.1)	0	0
<500	26 (54.1)	1 (12.5)	0
500-1000	11 (22.9)	6 (75)	0
>1000	10 (20.8)	1 (12.5)	4 (100)
Elevated ALK P (u/l)	25 (52.1)	8 (100)	4 (100)
Elevated GGT (u/l)	47 (97.9)	8 (100)	4 (100)
Serup protein (<6 gm/dl)	2 (4.2)	0	0
S. Albumin (<3.5 gm/dl)	7 (14.6)	2 (25)	0
S. Globulin (<2 gm/dl)	1 (2.1)	0	0
PT (> 15 s)	6 (12.5)	5 (62.5)	0
INR (>1.5)	2 (4.2)	2 (25)	0
Prolonged PT, INR	2 (4.2)	2 (25)	0

Normal values for total serum bilirubin≤1 mg/dl, AST: ≤40 U/L, ALT: ≤40 U/L, ALP: 1-9 years: 145-420, 10-11 years: 130-560, 12-13 years (M): 200-495, (F):105-420 U/L, GGT. AST: Asprtatate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transpeptidase, PT: Prothromin time, INR: International normalized ratio, AVH: Acute viral hepatitis

Mixed infection due to HAV+HEV and HAV+HBV were found in two cases (3.1%) each. Total serum bilirubin, AST, ALT, alkaline phosphatase and GGT (Gamma-glutamyl transpeptidase) values in the first group were 15.2, 1404.5, 1456, 336.7 and 90.17, respectively; whereas in the second group the values observed were 6.35, 206, 306, 467.5 and 56, respectively. All the biochemical parameters were significantly raised in the children affected with HAV and HEV coinfection ($p<0.05$).

DISCUSSION

We retrospectively studied 64 cases clinically diagnosed as AVH. The most common cause was found out to be HAV. Boys were more commonly affected than girls (M: F=44:20) in both enterically and parenterally transmitted infections. Similar findings were reported by other studies from India and outside [15-17].

Maximum number of children (62.5%) affected by hepatitis A were in the age group of 5-10 years. In this study, we found adolescents (10-15 years) were affected with HAV in 25% cases. A similar study from Chennai by Kamath et al. showed 61.6% and 15.9% of subjects were in the age group of 5-10 and 10-15 years, respectively [18]. The older age group involvement could be due to the shifting of epidemiological pattern of HAV infection. With the improving sanitary conditions, there is a recent decline in the anti-HAV antibody prevalence among school children, which predisposes older children to acquire the disease, occurrence of outbreaks and severe manifestation with ALF [19].

Although HAV infection was seen round the year in this study, maximum number of cases was admitted during the rainy season (July, August, and September). Jaundice, loss of appetite, vomiting, and fever were the common presenting symptoms. Atypical features such as splenomegaly, ascites, pleural effusion, and ALF were seen in 31.2%, 10.4%, 4.2%, and 4.2% children, respectively. Although very high serum AST and ALT levels (>1000 IU/L) were seen in 16 cases, serum bilirubin level more than 10 mg/dl was found in only one case (2.1%). Serum alkaline phosphatase levels were found to be increased in 52.1% cases, whereas raised serum Gamma-Glutamyl transpeptidase (GGT) levels were seen in 97.9% cases, which is a more specific indicator of cholestasis. Although hypoalbuminemia and coagulopathy (PT >15 s) were seen in 14.6% and 12.5% cases, respectively, ALF occurred in 4.1% with mortality in 2%. Rest of them recovered with conservative management. The deceased had very high total serum bilirubin levels (40.7 mg/dl), but moderate increase in transaminase levels (AST: 371 IU/L, ALT: 576 IU/L, ALK P: 237.7 IU/L).

In the current study, HEV was found to be the single cause of AVH in 6.25% cases. 50% were of age group 10-15 years with male predominance (75%) and maximum cases (50%) occurred in the rainy season. Clinical feature was almost similar to HAV group. Although very high serum levels of AST and ALT (AST: 2288±1203.1, ALT: 2653±1344.4) were seen, there was no complication and recovery was uneventful.

Interestingly, we found HBV to be the second most common cause of AVH in contrast to other studies [15-17]. This can be contributed to the following factors. First, many of the children were of poor socioeconomic status and from tribal communities. Poor coverage of vaccination program, high endemicity in certain groups, limited knowledge of preventing programs and lack of education may have contributed to it. Some studies have shown very high HBsAg positivity among tribal population of India [20]. Second, HEV infection in children is mostly asymptomatic or mild. Hence, they most probably did not need hospitalization. Male predominance, similar presenting symptoms as the other two groups, good recovery without any complications were the characteristic features. However, these patients need regular follow-up for the development of chronic hepatitis or carrier state.

Mixed infections were also seen in this study in the form of HAV+HEV and HAV+HBV; 2 case each. All the four cases recovered without any complications. Arora et al. in their study found mixed infection with HAV and HEV to be the most common cause of ALF in children (60%) [21]. Although some study say dual infection with HEV and other hepatotropic viruses to be associated with greater elevation of AST and ALT [22], similar conclusions could not be drawn from the present study due to small sample size.

One of the merits of the study is that very few studies had been reported from Eastern India regarding AVH in children. It has got limitations too. It was conducted in a tertiary care hospital among hospitalized children. Hence, the clinical profile may not be generalized to the community. Second, as this was a retrospective study, proper follow-up was not possible and the long-term outcome could not be studied. Further larger community-based studies are needed to know the sero-epidemiolgy of viral hepatitis in this part of the country.

CONCLUSION

AVH is a major public health problem in India. HAV, HBV, and HEV are prevalent and can cause sporadic or epidemic AVH. Although clinical features are similar, death and atypical presentations are more common in hepatitis A infection. Better sanitation, provision of clean drinking water, proper sewage disposal, and public education are the mainstays for prevention of HAV and HEV infection. Universal vaccination against HAV and HBV should be the focus of authorities to prevent morbidity and mortality due to these common pathogens.

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