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RESEARCH ARTICLE

CONTRIBUTION OF HEPATITIS VIRAL MARKERS IN CLINICAL CASES OF JAUNDICE AT A TERTIARY CARE CENTRE

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A R T I C L E I N F O

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A B S T R A C T

Introduction Acute viral hepatitis is caused by a group of five hepatotropic viruses namely types A, B, C, D and E. These hepatotropic viruses are serious public health concern. This study was conducted to study differential prevalence of these hepatitis viruses in different age groups.

Methodology A prospective study was conducted over a period of one year. Subjects were divided into study (n=800) and control (n=200) arm. Inclusion and exclusion criteria were defined and subjects were distributed age and sex wise. All the samples in study and control group were tested for IgM anti HAV, HBsAg, IgM Anti HCV and IgM anti HEV. Statistical Package for Social Sciences (SPSS), version 10.0 was used for statistical analysis.

Results The overall seroprevalence of acute viral hepatitis in study arm was 21.3% as compared to 8.5% in control arm. 0-10 year age group of the study arm had cumulative positivity of 25.7% with highest seropositivity for IgM anti HAV (65.4%). In 11-20 yrs of age group out of the total positive cases (23.6%), IgM anti HCV accounted for majority of cases (38.5%). For 21-30 and 31-40 years of age, the maximum contribution was by HEV i.e. 36.9% and 50% respectively. This was followed by HBV in both age groups (26.4% and 25%) respectively. In >40 yrs of age group, HBsAg was positive in 50% of the cases and IgM anti HCV was positive in another 50%.

Conclusions HAV is still the predominant infection of childhood in developing countries but age of acquisition is gradually shifting towards adolescence. HCV mainly contributes to infection in young adults but most cases are asymptomatic and hence underreported. HEV and HBV mainly contribute to infections in adults due to continued risk of exposure with age. Vaccination programs need to be consolidated for HBV and HAV.

INTRODUCTION

Acute viral hepatitis (AVH) is inflammation of the liver caused by a group of five hepatotropic viruses namely types A, B, C, D and E.[1] The condition can be self-limiting or can progress to fibrosis, cirrhosis or liver cancer.[2]These hepatotropic viruses are serious public health concern because of the burden of illness and associated mortality with potential for outbreaks. [2] Hepatitis A and E are common causes of enterically transmitted hepatitis spread through contaminated food or water.[3] Hepatitis B, C and D usually occur as a result of parenteral contact with infected body fluids.[3]This may include receipt of contaminated blood or blood products, invasive medical procedures using contaminated equipment .[4] Hepatitis B virus can also be transmitted from mother to baby at birth and by sexual contact. [4]

Acute infection may be asymptomatic, or may include symptoms such as jaundice, dark urine, fatigue, nausea; vomiting and abdominal pain.[5] Hepatitis B and C virus lead to chronic disease and together are the most common cause of liver cirrhosis and liver carcinoma [5.] Markedly raised amino transferase values (>1000U/L) and hyperbilirubinemia are observed.[6] Severe cases of acute hepatitis may progress rapidly to acute liver failure, marked by poor hepatic synthetic function.[7] The diagnosis of acute viral hepatitis is based on serological demonstration of viral markers namely HBsAg, IgM anti HAV, IgM anti HCV and IgM anti HEV antibody.[7] Improved sanitation with strict personal hygiene may help prevent transmission of HAV and HEV . [8] Prophylaxis for HBV and HCV includes general methods like avoidance of promiscuous sex, injectable drug abuse and direct or indirect contact with blood or blood products.[8] Specific prophylaxis like active immunization with HAV vaccine, hepatitis B immunoglobulin (HBIG) and recombinant HBV vaccines are also recommended.[9] Treatment for acute hepatitis caused by HAV, HEV and HBV is necessarily supportive in nature.[10] acute hepatitis C is detected infrequently but once diagnosed; it warrants early interferon (IFN) therapy. [11]Specific treatment for chronic hepatitis B include pegylated interferon (PEG-IFN) alfa-2a and oral nucleoside or nucleotide analogues.[12]

Interferon based therapy in combination with ribavirin is used for treatment of chronic hepatitis C.[13]

METHODOLOGY

This Study was conducted in the Department of Microbiology at Lady Hardinge Medical College, New Delhi. This was a prospective study done over a period of one year from January to December 2008. 800 Subjects were divided into study and control arms. Study arm had 600 patients presenting with clinical jaundice attending the outpatient departments of various specialties in Kalawati Saran Hospital, New Delhi. Inclusion criteria were fever and recent onset of jaundice (<6months), serum bilirubin level >2.5 mg/dl with five fold increase in serum transaminase levels. Exclusion criteria were either duration of illness more than six months, history of chronic liver disease or jaundice, acute fatty liver or intrahepatic cholestasis. Control Group had 200 age and sex matched subjects. Blood samples received in the serology section of department of Microbiology from patients satisfying the inclusion criteria were scrutinized. The sera were separated and stored in the deep freeze at -70°C until tested for the viral markers.

All the samples in study and control group were tested for IgM anti HAV, HBsAg, IgM Anti HCV and IgM anti HEV using commercially available kit manufactured by Biokit S.A. Spain based on ELISA methodology. Statistical Package for Social Sciences (SPSS), version 10.0 was used for statistical analysis. The chi-square test was used to compare discrete values between groups. The means, percentages were calculated and compared between the study and the control group by using Student's't-test' and chi-square test respectively. A *p* value of less then 0.05 was considered significant.

Table 1 Age and sex distribution of subjects in Study and control arms

Age Group	Study arm (n=600)			Control arm (n=200)		
	Male (%)	Female (%)	Total (%)	Male (%)	Female (%)	Total (%)
0-10 yrs	133 (62.1)	81 (37.8)	214 (35.7)	40 (56.3)	31 (43.6)	71 (35.5)
11-20 yrs	62 (56.3)	48 (43.6)	110 (18.3)	21 (58.3)	15 (41.6)	36 (18)
21-30 yrs	87 (66.9)	43 (33)	130 (21.6)	32 (74.4)	11 (25.5)	43 (21.5)
31-40 yrs	34 (50.7)	33 (49.2)	67 (11.1)	15 (68.1)	7 (31.8)	22 (11)
>40 yrs	46 (58.2)	33 (41.7)	79 (13.1)	13 (46.4)	15 (53.5)	28 (14)
Total	362 (60.3) M:F	238 (39.6) 1.5:1	600	121 (60.5) M:F	79 (39.5) 1.5:1	200

OBSERVATIONS AND RESULTS

The patients in study arm were distributed age wise into 0-10, 11-20, 21-30, 31-40 and >40 years of age groups. Sex wise distribution of the study arm was done for all age groups. Accordingly, age and sex matched controls were taken. The study arm comprised of 362 male and 238 female patients. The control arm (n=200) comprised of 121 male and 79 female patients. The mean age in the study arm was 20.2 years while in the control arm it was 19.65 years. The difference between the mean age of study and control group was not statistically significant (p>0.05). Male predominance was seen overall as well as in different age groups in both study and control arms.

Table 2 Contribution of hepatitis viral markers in infectious hepatitis cases

(Studyarm n=600)

Age Group	Total Tested	Total Positive (%)	IgM anti HAV (%)	HBsAg (%)	IgM anti HCV (%)	IgM anti HEV (%)
0-10 yrs	214	55 (25.7)	36 (16.8)	6 (2.8)	11 (5.1)	2 (0.9)
11-20 yrs	110	26 (23.6)	8 (7.2)	5 (4.5)	10 (9)	3 (2.7)
21-30 yrs	130	38 (29.2)	6 (4.6)	10 (7.6)	8 (6.1)	14 (10.7)
31-40 yrs	67	4 (5.9)	0	1 (1.4)	1 (1.4)	2 (2.9)
> 40 yrs	79	5 (6.3)	0	2 (2.5)	3 (3.7)	0
Total	600	128(21.3)	50 (8.3)	24 (4)	33 (5.5)	21 (3.5)

Table 3 Contribution of hepatitis viral markers in Control arm (n=200)

Age Group	Total Tested	Total Positive	IgM anti HAV (%)	HBsAg (%)	IgM anti HCV (%)	IgM anti HEV (%)
0-10 yrs	71	8 (11.2)	2 (2.8)	2 (2.8)	2 (2.8)	2 (2.8)
11-20 yrs	36	5 (13.8)	2 (5.5)	1 (2.7)	1 (2.7)	1 (2.7)
21-30 yrs	43	2 (4.6)	0	1 (2.3)	0	1 (2.3)
31-40 yrs	22	1 (4.5)	0	0	0	1 (4.5)
> 40 yrs	28	1 (3.5)	0	1 (3.5)	0	0
Total	200	17 (8.5)	4 (2)	5 (2.5)	3 (1.5)	5 (2.5)

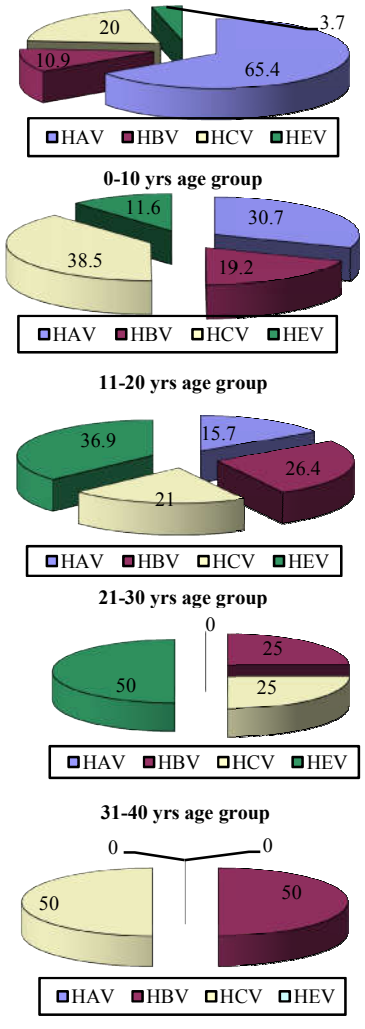

Figure 1 Contribution of hepatitis viral markers in infectious Hepatitis cases for the study arm (**Study arm n=600)**

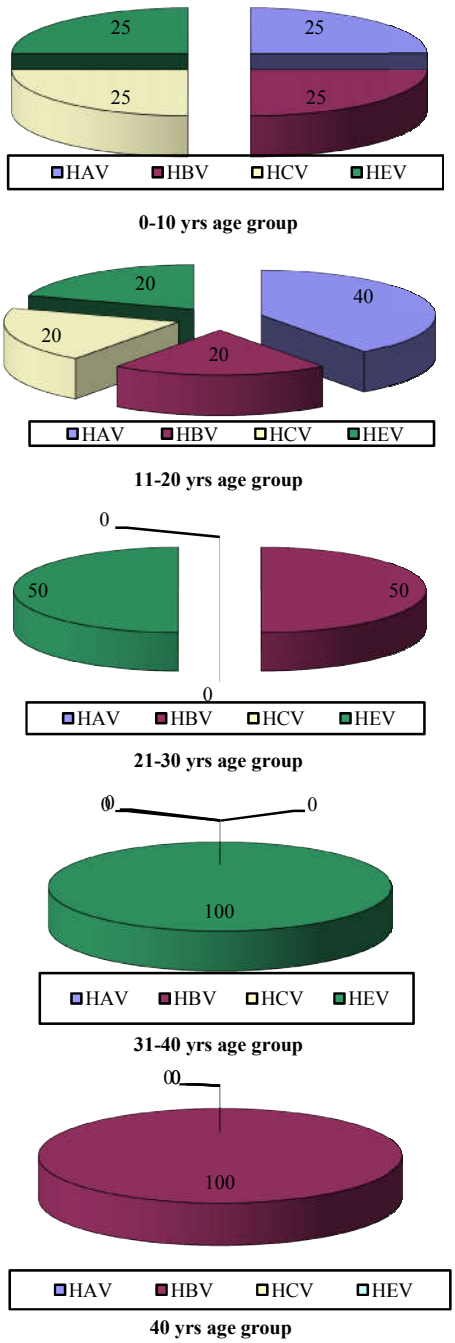

Figure 2 Contribution of hepatitis viral markers for the control arm
Control arm (n=200)

The overall seroprevalence of acute viral hepatitis in study group was 21.3%. In the study arm among 0-10 yrs of age group cumulative seropositivity was 25.7% with highest seropositivity for IgM anti HAV (65.4%). This was followed by IgM anti HCV, HBsAg and IgM anti HEV, the contribution being 20%, 10.9% and 3.7% respectively. Among the 11-20 yrs of age group cumulative seropositivity was 23.6% with highest seropositivity for IgM anti HCV (38.5%) followed by IgM anti HAV (30.7%), HBsAg (19.2%) and IgM anti HEV (11.6%). In the 21-30 yrs of age group cumulative seropositivity was 29.2% with highest seropositivity for IgM anti HEV (36.9%), followed by HBsAg (26.4%), IgM anti HCV (21%) and IgM anti HAV (15.7%). In 31-40 yrs of age group with a cumulative seropositivity of 5.9%, IgM anti HEV accounted for half the cases (50%), followed by HBsAg (25%), IgM anti HCV (25%) and none of the cases were positive for IgM anti HAV. In >40 yrs of age group, HBsAg was positive in 50% of the cases and IgM anti HCV was positive in another 50%.

In the control group (n=200), the overall seropositivity was 8.5%. Among the 8 positive cases in 0-10 yrs of age group, all the four serological markers were equally distributed (25%). In 11-20 yrs of age group, out of the total positive cases (5), IgM anti HAV accounted for maximum number of cases (40%) followed by HBsAg, IgM anti HCV and IgM anti HEV. Out of total positive cases in 21-30 yrs of age group, only 2 markers were positive, HBsAg (50%) and IgM anti HEV (50%). Out of total positive cases in 31-40 yrs of age group, only IgM anti HEV (100%) was positive. In > 40 yrs age group, only HBsAg (100%) was positive.

DISCUSSION

Acute viral hepatitis in India is caused by five well described hepatotropic viruses which are divided into enteral and parenteral groups based on mode of transmission.[5] HAV and HEV are enterically transmitted through orofecal route while hepatitis B, C & D viruses are parenterally transmitted.[6] Other viruses that can cause hepatic inflammation include Epstein Barr Virus (EBV), Herpes Simplex Virus (HSV), Mumps Rubella, Yellow fever virus and Adeno virus.[14] Acute viral hepatitis is a global public health concern associated with significant mortality and morbidity.

In the study arm in 0-10 yrs of age group, maximum cases were positive for IgM anti HAV (65.4%) indicating hepatitis A as predominantly a childhood infection. The mean age at which hepatitis A virus infection has been shown to occur, tends to differ in developing and developed countries with infections occurring at younger age in developing countries.[15] There is almost universal exposure in infancy and childhood.[16] Passive transmission of maternal antibody protects the neonate, but protection wanes during infancy.[16]Young children are ideal orofecal transmitters of infection because of their low immunity status[17]. In the developing world, where sanitation is poor, infection contributes to high endemicity pattern.[16] A recent study postulated that the main cause of transmission of HAV was improper waste disposal leading to contamination of water sources.[18] Overflowing rain water contaminates potable water supply leading to the outbreaks.[18]A recent study from Delhi, has reported that the frequency of HAV infection among children has increased from 8.4 to 12.3% over a period of five years.[19] Outbreaks are observed in child care centers and schools and occasionally large food borne epidemics have been reported. Disease acquired in early childhood has large number of asymptomatic and anicteric cases making case identification difficult[16].According to a recent study done at Pune, India, virtually 100% of children are infected by late childhood.[20]Safe and effective hepatitis A vaccines have been available since 1992, but are significantly underutilized. In countries of intermediate endemicity, WHO recommends large-scale childhood vaccination to be considered as a supplement to health education and improved sanitation.[21] Among 11-20 yrs of age group of the study arm cumulative seropositivity was 23.6% with IgM anti HCV seropositivity at

38.5% followed by IgM anti HAV at 30.7%. A recent mortality and morbidity report by CDC (2011), Massachusetts reported an increase in seroprevalence rate of HCV in 15-24 year age group during 2002 to 2006.[22] Injection drug use (IDU) was the most common risk factor for HCV transmission. [22] The highest reported age-specific incidence of acute hepatitis C in the United States is now among young adults.[23] A study reviewed patients suspected of acute viral hepatitis and the highest seroprevalence of IgM anti HCV was noted in 10-20 years of age group (6.9%).[24] The high incidence of HCV in young adults is attributed to increased risk of exposure in this age group. HCV is at least 10 times more infectious than HIV.[25]The risk of HCV transmission by needle stick injury is 3%–10% as compared to 0.3% for HIV .[25]Moreover, contaminated needles/syringes contribute significantly to blood-borne HCV transmission.

In recent years, there has been an emerging epidemic of HCV infection among young people who inject drugs (PWID)[26]. Also, tattooing procedures undertaken by young adults could be an added risk factor as postulated by some studies.[27]

Among 11-20 years of age group of study arm, highest seropositivity was for HCV followed by HAV (30.7%). 11-20 years of age group of control arm had maximum seroprevalence for HAV. Our findings are supported by a study from Delhi where trends of acute sporadic viral hepatitis A over a period of five years in patients aged 13-20, 21-30 and >30 yr showed an increase in proportion of HAV infections by three folds.[28] These findings are attributed to the fact that the epidemiologic pattern of hepatitis A infection is currently changing in developing countries with improvements in socioeconomic conditions, public health programs and sanitation. Hence, there has been a gradual shift in age of acquiring the infection from early childhood to adulthood.[20] In most developed countries sanitation and hygienic conditions are generally good and infection rates in children are generally low, shifting peak rates of infection to adolescence and young adulthood.[28] Concomitantly, there is an increase in symptomatic cases and in severe clinical outcomes including liver failure.[20]

Our study postulated that both in 21-30 yrs and 31-40 years of age group HEV contributed for maximum number of cases i.e. (36.9% and 50%), followed by HBsAg (26.4% and 25%). Similar findings were observed in control arm for 21-30 years of age group. It has been widely reported that HEV primarily affects young adults between 15-40 yr of age in endemic region.[29,30] Kaur *et al* (New Delhi, 2002) reviewed 306 patients with acute viral hepatitis and found that HEV was more often seen in 21-30 years (32.2%) and very few sera was positive in children.[31] Another study studied 148 patients with acute viral hepatitis and recorded higher seropositivity of HEV infection among adults (56.1%) compared to children (34.78%). [32]HEV infection is mostly asymptomatic and anicteric in children under nine years of age in endemic hepatitis.[33] Low standards of sanitation promote the transmission of the virus by orofecal route. Hepatitis E is usually a self limiting disease with low rate of fulminant hepatic failure. However, when this infection occurs in pregnant women, the consequences are particularly disastrous.[34] pregnant women particularly those in second and third trimesters are more frequently affected[34]. However, in our study only 15 pregnant women were reported and none were reported to be positive for HEV.

For 21-30 and 31-40 years of age, the maximum contribution was by HEV followed by HBV. The high prevalence rates of HBsAg in 21-30 years group is due to increased sexual activity, promiscuity and intravenous drug abuse among adults.[35]HBV is transmitted through percutaneous and parenteral contact with the infected blood, body fluids etc.[35] Increased exposure to these risk factors could be responsible for increased seropositivity of HBsAg in this age group.

In >40 yrs of age group, HBsAg was positive in 50% of the cases and IgM anti HCV was positive in another 50%.Moreover for >40 years age group of control arm all cases were contributed by HBV. Many studies have demonstrated that acute hepatitis occurring in >40 years of age end up with chronicity.[36, 37] Initial HCV infection is often asymptomatic and can progress insidiously. Approximately 75% of infected individuals are unaware of the infection and of these, approximately 70% to 85% will not clear the virus and remain chronically infected. [36]Davis *et al* found that patients older than 60 years of age affected with HCV need urgent attention to prevent complications.[37] Age is a significant factor conversely associated with sustained virological response following treatment.[36]These patients are not only at risk of developing complications from the infection but also at risk of occult transmission.

Another finding substantiated in our study was that no cases were contributed by HAV in >30 years of age in study and >20 years of age in control arm. HAV is still the predominant cause of acute viral hepatitis among children. High numbers of cases were enrolled among 0-10 years of age at our pediatric hospital is another reason for this finding.

CONCLUSIONS

HAV is still the predominant infection among children in developing countries, but implementation of public health strategies, has gradually shifted the age of acquisition of HAV towards adolescence. HAV vaccine is widely available but still under utilized so it should be incorporated in national immunization program.

HCV mainly contributes to infection in young adults but most of the cases are asymptomatic and disease is underreported thus significantly increasing the disease burden. HEV and HBV mainly contribute to infections in adults due to continued risk of exposure with increasing age. Vaccination programs need to be strengthened for HBV and HAV.

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