Viral hepatitis in India: Current status

M Irshad*, Dhananjay Singh Mankotia, Khushboo Irshad and Priyanka Gupta
Division of Clinical Biochemistry, Department of Laboratory Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

Abstract

Background: Viral hepatitis is a major cause of liver diseases and poses a serious public health problem throughout the world including India.

Objectives: Present study was planned to investigate the current status of viral hepatitis in patients with different liver and renal diseases.

Methods: A total number of 1043 patients, selected from an adult population with both the sexes, were included in this study plan. After clinical examination, their sera were analyzed for the presence of different hepatitis viral markers. The diagnosis of acute infection was based on the presence of IgM type antibody for hepatitis A, B, D & E infections. HCV-RNA or total anti-HCV was used for the diagnosis of HCV infection.

Results: We found the presence of hepatitis A virus (HAV) infection to be in 1-2% cases. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections were recorded to be the major cause of acute and chronic liver diseases. At the same time, hepatitis E virus (HEV) was responsible for causing acute liver diseases without showing its presence in chronic liver diseases. Hepatitis D virus (HDV) infection was not detected in this group of patients. Occurrence of co-infection was recorded merely with HBV-HCV without any other type of co-infection. A clinical follow-up of patients having co-infection or super-infection demonstrated a relatively more derangement of liver functions in the patients.

Conclusion: All types of hepatitis viral infections are prevalent in Indian patients’ populations. The relative incidences of these infections vary slightly from place to place.

Introduction

Viral hepatitis is caused by a number of viruses some of which have already been characterized and named as hepatitis viruses A, B, C, D, E and G, respectively [1-3]. In addition, there are patients who are not accounted by these viral infections but show all clinical symptoms suggestive of viral hepatitis. Such cases are assumed to be caused by a group of viruses classified as non-A-G hepatitis viruses. Nearly 15% patients of viral hepatitis belong to this group. These viruses need to be characterized for their molecular structure and types of disease caused. Viral hepatitis is a serious problem in India too with a high proportion of liver ailments caused by hepatitis viruses [4-6]. Based on various studies, all types of known and unknown viruses causing hepatitis have been reported in Indian populations [7].

Some of these viral infections have sufficiently long incubation period and remain asymptomatic in initial phase of disease. At the same time, it is not possible to detect any serological marker during window period. Today, there are assays available to diagnose hepatitis viral infections with high accuracy during total course of disease [8-10]. These assays are able to detect viral markers both in an early phase of the disease, as well as during the window period. These diagnostic assays focus mainly on detecting viral nucleic acid in addition to serological markers. Also, the newly developed assay systems can differentiate between the past and present infection [11-13]. A combination of both serology and nucleic acid based assays help in early detection and accurate diagnosis of infection.

The previous reports have demonstrated the relative prevalence of different viral infections in various categories of liver diseases including acute/chronic liver diseases, cirrhosis of liver and hepatocellular carcinoma (HCC) from different parts of our country [7,14,15]. All these reports clearly indicate the prevalence of all types of hepatitis viral infections that present from mild and asymptomatic form to severe liver ailments requiring emergency treatment. In addition, occurrence of water borne epidemics of hepatitis E viral infections is also not uncommon in this country [16,17]. Although there has been a decline in occurrence of such epidemics in last few years, however, it cannot be completely ruled out even today.

In view of viral hepatitis being a serious public health problem in India, it was assumed worth to conduct studies to assess the current status of viral hepatitis in this country, particularly with introduction of new and advanced diagnostic assays in this area. Therefore, we planned to find out the relative prevalence of hepatitis viral infections in different types of liver and renal diseases using sensitive and specific assay systems including higher generation immunoassays and PCR techniques. Sera from a large population of patients under each category of disease were analyzed to know the status of each individual type of infection as well as co-infections in these groups of patients.

Material and methods

Patients and blood samples

Total number of 1043 patients were included in the present study after obtaining their informed consent. They belonged to both the sexes and adult age group. Application of diagnostic criteria indicated 191
Irshad M (2018) Viral hepatitis in India: Current status

Institutional Ethics Committee of the concerned place of work. Venous blood was taken was diagnosed by serum creatinine level of more than >1.8 mg/dL after the basis of clinical, histopathological and radiological criteria. CKD of acute hepatitis. Patients with cirrhosis and HCC were diagnosed on intake. Fulminant hepatic failure was diagnosed when the patients up. Cirrhosis patients were not found to have history of chronic alcohol evidence of chronic hepatitis on liver biopsy at the beginning of follow-up. Cirrhosis patients were not found to have history of chronic alcohol intake. Fulminant hepatic failure was diagnosed when the patients showed signs of hepatic encephalopathy within 4 weeks of the onset of acute hepatitis. Patients with cirrhosis and HCC were diagnosed on the basis of clinical, histopathological and radiological criteria. CKD was diagnosed by serum creatinine level of more than >1.8 mg/dL after 3 months in the absence of other factors [7].

Results of hepatitis viral markers are shown in Table 1. Based on analysis of the results, the presence of HAV infection, as indicated by IgM anti-HAV in serum, was noticed in 6 of 191 (3.1%) patients with AVH. Hepatitis B virus infection was diagnosed by the presence of HBsAg and IgM anti-HBc in serum. Presence of HBsAg in serum was recorded in 100 of 191 patients (52.4%) with AVH, 34 of 88 patients (38.6%) with FHF, 151 of 258 patients (58.5%) with CVH, 201 of 223 patients (90.1%) with cirrhosis and 34 of 69 patients (49.3%) with HCC. IgM anti-HBc, a marker indicating exclusively acute HBV infection, was detected in 25.5% cases with AVH, 29.8% cases with FHF, 19.9% cases with CVH, 7.9% cases with cirrhosis and none with HCC.

Three different diagnostic markers including anti-HCV antibodies, HCV-RNA and HCV-core antigen, were tested in sera for the diagnosis of HCV infection. Anti-HCV antibody, tested with third generation EIA, was detected in high proportion of patients with chronic liver diseases as compared to acute liver diseases. As such, anti-HCV was found positive in sera from 19 of 191 patients (9.9%) with AVH, 2 of 64 patients (3.1%) with FHF, 95 of 321 patients (29.6%) with CVH, 85 of 120 patients (70.8%) with cirrhosis and 34 of 76 patients (44.7%) with HCC. The presence of HCV-RNA in serum with replicating virus was noted in 14.3% cases with AVH, 1.6% cases with FHF, 80% cases with CVH, 43.3% cases with cirrhosis and 66.6% cases with HCC, respectively. HCV core antigen, reported to be another important marker of active HCV infection, was noted in 3.3%, 27.8%, 43.3%, 32.5%, and 27.3% with above liver disease groups, respectively. HDV infection, demonstrated by the presence of IgM-HDV antibodies in serum, was not detected in present panel of sera. On the contrary, HEV infection, showing its presence by IgM anti-HEV positivity in serum, was recorded in 28.4% patients with AVH and 41.9% with FHF. Similarly, TTV infection, detected by the presence of TTV-DNA in serum, showed a high prevalence in all categories of diseases.

Three different diagnostic markers including anti-HCV antibodies, HCV-RNA and HCV-core antigen, were tested in sera for the diagnosis of HCV infection. Anti-HCV antibody, tested with third generation EIA, was detected in high proportion of patients with chronic liver diseases as compared to acute liver diseases. As such, anti-HCV was found positive in sera from 19 of 191 patients (9.9%) with AVH, 2 of 64 patients (3.1%) with FHF, 95 of 321 patients (29.6%) with CVH, 85 of 120 patients (70.8%) with cirrhosis and 34 of 76 patients (44.7%) with HCC. The presence of HCV-RNA in serum with replicating virus was noted in 14.3% cases with AVH, 1.6% cases with FHF, 80% cases with CVH, 43.3% cases with cirrhosis and 66.6% cases with HCC, respectively. HCV core antigen, reported to be another important marker of active HCV infection, was noted in 3.3%, 27.8%, 43.3%, 32.5%, and 27.3% with above liver disease groups, respectively. HDV infection, demonstrated by the presence of IgM-HDV antibodies in serum, was not detected in present panel of sera. On the contrary, HEV infection, showing its presence by IgM anti-HEV positivity in serum, was recorded in 28.4% patients with AVH and 41.9% with FHF. Similarly, TTV infection, detected by the presence of TTV-DNA in serum, showed a high prevalence in all categories of diseases.
Analysis of 144 patients with CKD admitted for treatment, demonstrated the presence of mainly HBV & HCV infections of the known hepatitis-causing viruses. Whereas HBV was detected in approximately 4% cases, HCV infection on the contrary, was found in about 28% cases. Other hepatitis viruses like HAV, HDV or HEV could not show their presence in this disease group. The data shown in Table 2 demonstrate the presence of co-infection, i.e. simultaneous presence of two or more viral markers in serum. Co-infection with HBV and HCV was predominant in chronic liver diseases as compared to acute liver diseases. On the other hand, HBV and HEV co-infection was noted in higher percent cases of AVH as compared to other category of diseases. Presence of HBV with HEV was noted in 6.7% cases with CVH also, possibly due to exposure of these patients to contaminated water or food products. Other types of co-infections were very rare and insignificant in both liver and renal diseases. Co-infections usually result in severe form of infection causing serious diseases. The results from this study also point out towards a relation between co-infection and the severity of diseases. We observed more deranged organ function tests in patients carrying co-infection as compared to those with any single infection.

Discussion

After characterization of different hepatitis viruses in last few decades, studies were conducted to investigate the relative role of these viruses in causing acute and chronic liver diseases. At the same time, attempts were made to find out their role in outbreak of hepatitis in different countries and also their oncogenic potency in causing liver cancer. Today, hepatitis caused by these viruses is a serious public health problem throughout the world and WHO has developed a framework for the prevention and control of viral hepatitis [19]. Whereas HAV and HEV cause asymptomatic, benign and self-limited diseases in majority of cases [20,21], HBV and HCV infection may lead to serious liver diseases including cirrhosis of liver and hepatocellular carcinoma in significant proportion of cases [22,23]. In India, studies were conducted periodically and reported the presence of all these viruses in our populations [4,5,14]. They are responsible both for epidemic as well as sporadic cases of hepatitis in this country. Moreover, their pattern of disease causation as well as the final outcome of diseases was noticed more or less same as seen in other parts of the world, except their differential prevalence in patient's populations. An evolution tree of diagnosis in the area of hepatitis has ever prompted the researcher to have a new look at their status with induction of novel diagnostic assays. Since studies in last few years have inducted new techniques with high accuracy detecting presence of markers in window period as well as differentiating past from present infection, our team made fresh attempts to understand the recent status of hepatitis viral infection in different categories of liver and renal diseases in India. Present report includes a large population of patients with serious liver and renal diseases for treatment and describes the status of prevalence of hepatitis viral infection in these disease groups.

Based on the results of our study, it has been observed that HAV shows its presence in minor percentage (1-2%) of adult population. The previous reports, both from our centre as well as from other studies, demonstrate HAV to be a problem of children and development of protecting anti-HAV antibodies in large population by the age of 12 years [24]. This may be an important reason of protection against

### Table 1. Status of hepatitis viral infections in different liver and renal diseases

| Type of Infection | Viral Marker | AVH (n=191) | FHF (n=88) | CVH (n=321) | CIR (n=223) | HCC (n=76) | CKD (n=144) |
|-------------------|--------------|------------|------------|------------|-------------|------------|-------------|
|                   | No. tested   | +ve        | %age       | No. tested | +ve        | %age       | No. tested | +ve        | %age       | No. tested | +ve        | %age       | No. tested | +ve        | %age       |
| HBV               | 191          | 6          | 3.1        | 60         | 0          | 0          | 200        | 0          | 0          | 70         | 0          | 0          | 80          | 0          | 0          |
| HAV               | 149          | 38         | 25.5       | 47         | 14         | 29.8       | 156        | 31         | 19.9       | 114        | 9          | 7.9        | 14          | 0          | 0          |
| HCV               | 191          | 19         | 9.9        | 62         | 4          | 3.1        | 321        | 95         | 29.6       | 120        | 85         | 70.8       | 76          | 34         | 44.7       |
| HDV               | 58           | 14         | 24.1       | 64         | 1          | 1.6        | 85         | 68         | 80         | 30         | 13         | 43.3       | 9           | 6          | 66.6       |
| HEV               | 183          | 52         | 28.4       | 62         | 26         | 41.9       | 60         | 9          | 15         | 60         | 12         | 20         | ND          | ND         | ND         |
| TTV               | 90           | 45         | 50         | 24         | 9          | 37.5       | 114        | 45         | 39.5       | 66         | 31         | 46.9       | 13          | 6          | 46.2       |

### Table 2. Status of hepatitis viral co-infection in liver and renal diseases

| Co-infection | AVH | FHF | CVH | CIR | HCC | CKD |
|--------------|-----|-----|-----|-----|-----|-----|
| HBV + HCV    | 3.8%| 2.8%| 9.7%| 13.8%| 28.6%| 1.4%|
| HBV + HDV    | Nil | Nil | Nil | Nil | Nil | Nil |
| HBV + HEV    | 14.1%| 5.7%| 6.7%| Nil | Nil | Nil |
| HCV + HEV    | 3.7%| Nil | 8.3%| 1.6%| Nil | Nil |
| HBV + HCV + HEV | 1.8%| Nil | 3.3%| Nil | Nil | Nil |

(i) Co-infection of HBV & HCV is indicated by presence of IgM anti-HBc& anti-HCV in AVH & FHF and HBsAg / IgM anti-HBc and anti HCV in CVH, cirrhosis and HCC cases.
(ii) Co-infection of HBV, HCV & HEV is indicated by IgM anti-HBc with anti-HCV and IgM anti-HEV in acute cases and HBsAg/ IgM anti-HBc with these markers in CVH, cirrhosis and HCC cases.
(iii) % value was computed on the basis of total number of cases tested in each disease group.
HAV infection in adults. However, it is a common observation that co-infection of HAV with other hepatitis viruses(e), usually takes a formidable form causing very serious diseases [25,26].

We found presence of HBV infection both in acute as well as chronic liver diseases. Its presence was recorded in about one-fourth population of acute viral hepatitis cases. Similarly, HBV infection was quite common in patients with all types of liver diseases. However, its presence was noticed to be low in patients with CKD. HCV infection, which is responsible to cause chronic liver diseases, was recorded in high proportion of patients with CVH, cirrhosis and HCC. Acute liver diseases could not show HCV infection in significant number of cases. The prevalence of HCV infection was based on the analysis by combined assays including EIA and PCR detecting anti-HCV and HCV RNA. This finding is in total consonance with results reported from several other countries as well [2,11]. Similarly, HCV infection was recorded in about one-third of patients with CKD. Use of HCV core antigen could not show a direct relationship with other markers like anti-HCV and HCV-RNA and therefore, was not considered important for diagnostic purpose. Presence of HDV, HEV and TTV infection in all these disease groups is the same as reported earlier on several occasions [27,28]. Hepatitis viruses do not appear to change a scenario of endemicity in this country and so infect the population and cause diseases pattern determined by their molecular characteristics and host response to their invasion. In India, HEV is more popular for causing waterborne epidemics in certain pockets and during particular seasons [14]. Their sporadic invasion often remains benign until HEV becomes a part of co-infection or targets pregnant women where this infection manifests in serious diseases [29]. On a similar pattern, TTV infection, known hitherto as a possible component of unknown hepatitis viruses, is extensive in this country infecting large population but causing no symptoms [30]. Therefore, its routine diagnosis or the treatment of TTV infection is never taken seriously in India.

Conclusion

Present study, thus, concludes that viral hepatitis in India follows a pattern seen in many other regions of the world. Whereas hepatitis A is rarely noticed in adults, hepatitis B and C infections are responsible for causing both acute and chronic liver diseases in sizeable proportions of patients. Hepatitis E causes acute manifestation whereas HDV infection remains to be a rare entity in this country. Viral hepatitis is really a serious concern in India and needs a strategic control on global pattern.

Author contributions

Irshad M planned the study, wrote the manuscript and edited it. Rest other authors conducted the study and analyzed the data.

Conflict of interest statement

There is no conflict of interest among the authors.

Acknowledgments

The authors appreciate the infrastructure provided by All India Institute of Medical Sciences, New Delhi, India, for conduct of this study. Scholarship from Council of Scientific and Industrial Research (CSIR), New Delhi to DSM is also acknowledged.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, et al. (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 244: 359-362. [Crossref]
2. Bradley DW (1992) Virology, molecular biology, and serology of hepatitis C virus. Transfus Med Rev 6: 93-102. [Crossref]
3. Farci P, Gerin JL, Aragona M, Lindsey I, Crivelli O, et al. (1986) Diagnostic and prognostic significance of the IgM antibody to the hepatitis delta virus. JAMA 255: 1443-1446. [Crossref]
4. Irshad M, Acharya SK (1994) Status of hepatitis viral markers in patients with acute and chronic liver diseases in northern India. Intervirology 37: 369-372. [Crossref]
5. Tandon BN, Gandhi BM, Joshi YK (1984) Etiological spectrum of viral hepatitis and prevalence of markers of hepatitis A and B virus infection in north India. Bull World Health Organ 62: 67-73. [Crossref]
6. Acharya SK, Batra Y, Hazari S, Choudhury V, Panda SK, et al. (2002) Etiopathogenesis of acute hepatic failure: Eastern versus Western countries. J Gastroenterol Hepatol 17: S268-S273. [Crossref]
7. Irshad M, Singh S, Ansari MA, Joshi YK (2010) Viral Hepatitis in India: A Report from Delhi. Glob J Health Sci 2: 96.
8. Irshad M, Ansari MA, Irshad K, Lingaiah R (2013) Novel single-step multiplex real-time polymerase chain reaction assay for simultaneous quantification of hepatitis virus A, B, C and E in serum. J Gastroenterol Hepatol 28: 1869-1876. [Crossref]
9. Kodani M, Mixson-Hayden T, Drobeniec J, Kamili S (2014) Rapid and sensitive approach to simultaneous detection of genomes of hepatitis A, B, C, D and E viruses. J Clin Virol 61: 260-264. [Crossref]
10. Nyan DC, Swinson KL (2015) A novel multiplex isothermal amplification method for rapid detection and identification of viruses. Sci Rep 5: 17925. [Crossref]
11. Nübling CM, Unger G, Chudy M, Raia S, Löwer J (2002) Sensitivity of HCV core antigen and HCV RNA detection in the early infection phase. Transfusion 42: 1037-1045. [Crossref]
12. Allain JP, Cox L (2011) Challenges in hepatitis B detection among blood donors. Curr Opin Hematol 18: 461-466. [Crossref]
13. Mokhtari C, Marchadier E, Haim-Boukobza S, Jebaloui A, Tesse S, et al. (2013) Comparison of real-time RT-PCR assays for hepatitis E virus RNA detection. J Clin Virol 58: 36-40. [Crossref]
14. Acharya SK, Madan K, Duttagupta S, Panda SK (2006) Viral hepatitis in India. Natl Med J India 19: 203-217. [Crossref]
15. Mohana Lakshmi TM, Vaithilingam A, Franklin A, Reddy EP (2011) The prevalence of serological markers of viruses causing acute hepatitis in south Indian population. Int J Biol Med Res 2: 925-928.
16. Kumar S, Ratho RK, Chawla VK, Chakraborti A (2006) Virological investigation of a hepatitis E epidemic in Northern India. Singapore Med J 47: 769-773. [Crossref]
17. Arankalle VA, Chadha MS, Tsarev SA, Emerson SU, Risbud AR, et al. (1994) Seroepidemiology of water-borne hepatitis E in India and evidence for a third enterically-transmitted hepatitis agent. Proc Natl Acad Sci U S A 91: 3428-3432. [Crossref]
18. Irshad M, Mandal K, Singh S, Agarwal SK (2010) Torque teno virus infection in hemodialysis patients in North India. Int Urol Nephrol 42: 1077-1083. [Crossref]
19. WHO (2016) Prevention and Control of Viral Hepatitis Infection: Framework for Global Action. WHO. [Crossref]
20. Ciocca M (2000) Clinical course and consequences of hepatitis A infection. Vaccine 18: S71-S74. [Crossref]
21. Wedemeyer H, Pischke S, Manns MP (2012) Pathogenesis and treatment of hepatitis e virus infection. Gastroenterology 142: 1388-1397. [Crossref]
22. Pan CQ, Zhang JX (2005) Natural History and Clinical Consequences of Hepatitis B Virus Infection. Int J Med Sci 2: 34-60. [Crossref]
23. Bruno S, Facciotto C (2008) The natural course of HCV infection and the need for treatment. Ann Hepatol 7: 114-119. [Crossref]
24. Tandon BN, Gandhi BM, Joshi YK, Gupta H, Irshad M (1984) Subclinical hepatitis A in north Indian children. Lancet 1: 335-336. [Crossref]
25. Vento S (2000) Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. J Viral Hepat 7 Suppl 1: 7-8. [Crossref]
26. Pramoolsinapat C, Poovorawan Y, Hirsh P, Busagorn N, Attamaasiriik K (1999) Acute, hepatitis-A super-infection in HBV carriers, or chronic liver disease related to HBV or HCV. Ann Trop Med Parasitol 93: 745-751. [Crossref]
27. Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, et al. (2012) Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. *J Hepatol* 57: 1177-1185. [Crossref]
28. Irshad M, Joshi YK, Sharma Y, Dhar I (2006) Transfusion transmitted virus: A review on its molecular characteristics and role in medicine. *World J Gastroenterol* 12: 5122-5134. [Crossref]
29. Panda SK, Thakral D, Rehman S (2007) Hepatitis E virus. *Rev Med Virol* 17: 151-180. [Crossref]
30. Mankotia DS, Irshad M (2014) Cloning and expression of N22 region of Torque Teno virus(TTV) genome and use of peptide in developing immunoassay for TTV antibodies. *Virol J* 11: 96. [Crossref]