Original Research Article **Pathology**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

CLINICAL FEATURES AND RISK FACTORS FOR SEVERE COMPLICATIONS IN PATIENTS WITH HEPATITIS A VIRUS INFECTION FROM KAMRUP DISTRICT OF ASSAM, INDIA

PRIYANKA KASHYAP[1*], MANAB DEKA1, SANGIT DUTTA[2], MORTEZA KORDAFSHARI[1], MAJID KHANDOUZI[1] AND NAMRATA KUMARI[1]

[1]PhD Scholar, Department of Bioengineering and Technology ,Laboratory of Molecular Virology & Oncology, Gauhati University, Guwahati, Assam, India.
[2]Department of Medicine, Gauhati Medical College Hospital, Gauhati University, Guwahati, Assam, India
[3]Department of Bioengineering and Technology , Laboratory of Molecular Virology & Oncology, Gauhati University, Guwahati, Assam, India
[4]Department of Bioengineering and Technology , Laboratory of Molecular Virology & Oncology, Gauhati University, Guwahati, Assam, India

ABSTRACT

Viral hepatitis caused by hepatitis A virus (HAV) infection is a worldwide disease; is a self-limited disease which results in fulminant hepatitis and death in only a small proportion of patients (0.1-2.1%). This study analyzes the clinical severity in patients with acute HAV infection and investigates risk factors associated with two severe complications: prolonged cholestasis and fulminant hepatic failure.A total of 150 patients with an age ranging from 12-40 years were included in the study and were analyzed by age, sex, other hepatotropic viral infection, etc. The patients were selected on the basis of clinical investigation and biochemical profile including ALT, AST, PT (Prothrombin time), TB (Total Bilirubin), Total Protein. Age >30 years (p=1.00; OR= 6.6) was a risk factor for prolonged cholestasis and FHF. Peak PT (INR) ≥1.5 (p <0.0001; OR = 1.0) was a significant risk factor for prolonged cholestasis and FHF. Total Bilirubin, AST and ALT levels were not shown to be significant risk factors. Creatinine level was a risk factor (p=0.009; OR=1.0) for prolonged cholestasis and Fulminant hepatic failure FHF.

KEYWORDS: **Hepatitis A, Cholestasis, Fulminant, liver failure**

PRIYANKA KASHYAP
[1]PhD Scholar, Department of Bioengineering and Technology, Laboratory of Molecular Virology & Oncology, Gauhati University, Guwahati, Assam, India.

***Corresponding Author**

INTRODUCTION

Hepatitis A virus infection is generally self limited and symptoms vary from asymptomatic to death resulting from fulminant hepatitis. However a few patients may have prolonged or relapsing disease lasting up to 6 months [1,2].The risk of acute liver failure ranges from 0.015 to 0.5%, and the highest rates occur among young children and older adults with underlying chronic liver disease [3].HAV is a non enveloped RNA virus 27 to 32 nm diameter in size, with an icosahedral symmetry, which belongs to the genus *Hepatovirus* of the *Picornaviridae* family.HAV has a positive-polarity, single-stranded 7.5-kb genome that is organized similarly to those of the other picornaviruses . The 5'UTR is 734 to 740 nucleotides long and has a covalently linked virus-specific protein (VPg) rather than a cap structure [4]. The rest of the genome is composed of a single open reading frame with three distinct regions (P1, P2, and P3) and is translated as a single polyprotein of 2,225 to 2,227 amino acids. There is enough genetic diversity to define several HAV genotypes and subgenotypes. Genotype IA appears to be the agent responsible for the majority of hepatitis A cases worldwide [5,6] and has been isolated from all parts of the world. The endemicity of HAV infection varies according to regional hygienic standards worldwide and the highest prevalence of infection occurs in regions with the lowest socioeconomic levels [7]. Although most HAV patients have a favorable clinical course and spontaneous recovery, in a few patients the rates of hospitalization and severe complications appear to have increased substantially [8]. Severity of disease is strongly associated with age, with older children and adults often experiencing symptomatic disease [9, 10]. HAV infection can progress from simple jaundice to acute liver failure (ALF) [11]. Therefore, this study analyzes the clinical severity in patients with acute HAV infection and investigates risk factors associated with two severe complications: prolonged cholestasis and fulminant hepatic failure.

MATERIALS AND METHODS

Subjects

Patients with acute hepatitis A were enrolled from general OPD and Medicine Ward of Gauhati Medical College and Hospital (GMCH), Guwahati. It is a OPD based study. Acute hepatitis A was diagnosed by typical symptoms of acute hepatitis, by the presence of positive serum IgM anti-HAV associated with an elevation of serum aminotransferase levels five times above the upper normal limit. The cases which were found to be positive for IgM anti-HAV were further confirmed by HAV detection PCR spanning a region of 154 b.p. for VP1 region of the HAV genome. The exclusion criteria for selection of the cases included other etiologies of acute hepatitis like acute hepatitis B virus infection, hepatitis C infection, alcoholic, professional blood donors, high risk group like IV drug abusers, autoimmune hepatitis.The ethical committee reg no. is GUEC-09/2015

Inclusion and exclusion criteria for patient enrollment

The patients who were clinically diagnosed as acute viral hepatitis, fulminant hepatitis, Cholestasis on the basis of diagnostic criteria were included in the present study. The liver disease patients, who were associated with high-risk group like intravenous drug abusers, chronic renal failure, thalassemia, haemophilia, diabetes mellitus, psychiatric illness, and confection with other viruses, were excluded from the study. The G.U. Ethics committee registration no is GUEC-09/2015.

Study Design

A total of 150 patients with an age ranging from 12- 40 years were included in the study between the period 2012 to 2014 and were analyzed by age, sex, other hepatotropic viral infection like hepatitis B or hepatitis C, significant alcohol intake, duration of hospital stay, serum biochemistry, and coagulation test at admission and most severe clinical course. The patients were selected on the basis of clinical investigation and biochemical profile including ALT (alanine transaminase), AST (aspartate aminotransferase), PT (Prothrombin time) ,TB (Total Bilirubin),Total Protein (TP). In this study, prolonged cholestasis was defined as that with total bilirubin level ≥5 mg/dL lasting for more than 4 weeks after admission [12]. Acute liver failure according to the widely accepted definition of acute liver failure that states there would be evidence of coagulation abnormality, usually a prolongation of PT by INR ≥1.5 or prothrombin time >15 seconds, and any degree of mental alteration (encephalopathy) in a patient without pre-existing cirrhosis and with an illness with duration <26 weeks [13]. The clinical conditions of patients with complications were compared with those without complications and the association of clinical risk factors with each severe complication was also analysed. This study was approved by the Gauhati University Ethics Committee and patient consent was also taken from the study subjects.

Statistical analysis

Statistical analysis was performed by the standard methods using SPSS computer software (Version 13, SPSS Inc., and Chicago, IL, USA). The results were presented as mean±standard deviation or number of instances (percent). Fisher's exact test was used to compare clinical features according to the presence of complications. Student's t-test was used for continuous variables. Associations between clinical features and HAV disease severity were calculated as odds ratio (OR) with 95% confidence intervals (CIs). p-values of <0.05 were considered statistically significant.

RESULTS

Demographic data of hepatitis A patients

A total of 150 HAV confirmed cases were included in the study. The male and female ratio was found out to be 3:1 and so the male gender was predominant (76%). It was seen that the confirmed cases of HAV infection belonged mostly to the young adults in this region and so Hepatitis A frequently occurred in the young adults where mean age was calculated to be 25 years. This

study shows that the young adults are seen to be more susceptible to hepatitis A infection in this region. Fulminant hepatic failure developed in 0.02% of the Hepatitis A patients (Table II). Among the 150 HAV patients, 0.13 (1.3%) patients had prolonged cholestasis during admission and 0.01 (1%) had relapsing hepatitis during admission.

Clinical manifestations

The clinical and the laboratory characteristics of Hepatitis A cases are summarized in Table I and Table III. Fever was most frequent symptom and jaundice was observed in 68% of the patients. Among the laboratory characteristics, ALT mean value was 468 IU/L, with a total bilirubin value of 5.37 mg/dl in the acute HAV cases.

Comparison of clinical characteristics of patients

Symptoms and signs	Frequency (%)
Nausea	60(90/150)
Vomiting	64(96/150)
Fatigue	44(66/150)
Fever	73.3(110/150)
Loss of appetite	60(90/150)
Jaundice	68(102/150)
Arthralgia	6 (9/150)
Diarrhea	41.3(62/150)
Skin rash	16(24/150)

Table I
Symptoms and signs of hepatitis A (n = 150)

Cases	Frequency (case/total)
Acute hepatitis A	0.83 (125/150)
Hepatitis A with cholestasis	0.13 (20/150)
Relapsing hepatitis A	0.01 (2/150)
Fulminant Hepatic Failure (FHF)	0.02 (3/150)

Table II
Stratification of the HAV cases (n = 150)

Parameter	Acute Hepatitis A	HepatitisA with cholestasis	Fulminant Hepatic Failure (FHF)
Age	25 ± 7.12	28 ± 12.41	28 ± 10.44
Sex ratio	29:6	7 :3	2:1
ALT(IU/L) ≤ 40	468 ± 171.24	923 ± 192.21	4763.5 **±** 744.58
AST(IU/L) ≤ 40	252.33 ± 220.94	747.7 ± 168.34	4416 ± 642.05
Prothrombin time(INR) (2.0 – 3.0)	1.20 ± 0.60	2.36 ± 2.12	8 ± 0.56
Total Bilirubin(mg/dl) 0.4-1.2	5.37 ± 0.84	16.24 ± 11.22	18.40 ± 11.30
Total protein (gm/dl) 6.5-8	7 ± 1.98	7.95 ± 1.16	8.1 ± 0.42

Table III
Clinical and laboratory characteristics of hepatitis A cases (n = 150)Comparison of clinical characteristics of patients with different HAV infection cases

Variable	Prolonged cholestasis	Non cholestasis	p value
Age	28 ± 8.34	25 ± 7.12	**0.03**
Sex	7 : 3	29 : 6	
Laboratory values at admission			
Haemoglobin (g/dl)	12.9 ± 2.1	12.32 ± 2.65	0.37
Prothrombin time (INR)	2.36 ± 2.12	1.20 ± 0.60	**< 0.0002**
Total Bilirubin (mg/dl)	16.24 ± 11.22	5.37 ± 0.84	**< 0.0001**
AST (IU/L)	747.7 ± 168.34	252.33±220.94	**< 0.0001**
ALT (IU/L)	923 ± 192.21	468 ± 171.24	**< 0.0001**
Creatinine (mg/dL)	0.90 ± 0.26	0.98 ± 0.38	0.28
Laboratory values at peak time			
	12.9 ± 2.1	12.32 ± 2.65	0.35
rothrombin time (INR)	3.2 ±2.8	1.5 ± 0.9	**< 0.0001**
Total Bilirubin (mg/dl)	23.64±12.18	12.07±2.90	**< 0.0001**
AST (IU/L)	3230±121.23	3100±324.1	0.07
ALT (IU/L)	4017±781.4	2670±564.3	**< 0.0001**
Creatinine (mg/dL)	1.2±0.35	0.9±0.4	**0.0019**

Among the 150 patients, three severe forms of acute HAV complications occurred as prolonged cholestasis in 20 patients (0.13%) and fulminant hepatic failure (FHF) in 3 patients (0.02%). Table IV shows clinical characteristics of acute HAV infection patients with prolonged cholestasis in comparison to those without cholestasis. Patients with prolonged cholestasis were Older but there was no significant correlation with patients without cholestasis. They also had significantly prolonged PT (INR) (p<0.0002) and PT (INR) >1.5 at admission. The patients with prolonged cholestasis had significantly higher ALT and AST values than HAV patients without cholestasis (p<0.0001).

Table V
Comparison of Clinical Characteristics of Acute HAV Infection Patients with the FHF patients((Bold values represent significant risk).

	HAV caused FHF	Acute HAV	p value
Age	28 ± 10.44	25 ± 7.12	0.47
Sex	2:1	29 : 6	
Laboratory values at admission			
Haemoglobin (g/dl)	7.1 ±2.95	12.32 ± 2.65	0.001
Prothrombin time (INR)	8 ± 0.56	1.20 ± 0.60	< 0.0001
Total Bilirubin (mg/dl)	18.40 ± 11.30	5.37 ± 0.84	< 0.0001
AST (IU/L)	4416 ± 642.05	252.33±220.94	< 0.0001
ALT (IU/L)	4763.5 **±** 744.58	468 ± 171.24	< 0.0001
Creatinine (mg/dL)	2.4**±** 0.7	0.98 ± 0.38	< 0.0001
Laboratory values at peak time			
Haemoglobin (g/dl)	7.1 ±2.95	12.32 ± 2.65	0.001
Prothrombin time (INR)	8 ± 0.56	1.5 ± 0.9	< 0.0001
Total Bilirubin (mg/dl)	26.4 ± 0.8	12.07±2.90	< 0.0001
AST (IU/L)	4628 ± 612.8	3100±324.1	< 0.0001
ALT (IU/L)	4798 ± 621.7	2670±564.3	< 0.0001
Creatinine (mg/dL)	2.4**±** 0.7	0.9±0.4	< 0.0001

Table V shows comparison of clinical characteristics of acute HAV infection patients with HAV caused FHF patients. Patients with FHF had a mean age of 28 years and were older compared to acute HAV patients. FHF patients had significantly lower haemoglobin level and significantly very high Prothrombin time, Total Bilirubin, AST , ALT and creatinine levels as compared to acute HAV patients during admission and also during peak time.

Clinical risk factors associated with hepatitis A disease severity

Statistical analysis revealed several clinical risk factors for the three severe complications in patients with acute HAV infections (Table VI). Age >30 years (p=1.00; OR= 6.6) was a risk factor for prolonged cholestasis and FHF. Peak PT (INR) ≥1.5 (p <0.0001; OR = 1.0) was a significant risk factor for prolonged cholestasis and FHF. Total Bilirubin, AST and ALT levels were not shown to be significant risk factors. Creatinine level was a risk factor (p=0.009; OR=1.0) for prolonged cholestasis and FHF.

Table VI
Risk Factors Associated with Three Major Complications of Acute HAV Infection (Bold values represent significant risk ; OR Odds ratio; CI confidence interval).

Variable	Prolonged cholestasis(20)	FHF (3)	p value	OR (95%CI)
Age	28 ± 8.34	28 ± 10.44	1.00	**1.10**
Age >30 years	5 (0.25)	2 (0.66)	0.3	**6.6**
Prothrombin time (INR)	2.36 ± 2.12	8 ± 0.56	**0.0002**	**0.07**
Prothrombin time (INR) ≥1.5	4(0.2)	3(0)	**<0.0001**	**1.0**
TotalBilirubin(mg/dl)	16.24 ± 11.22	18.40± 11.30	**0.7**	**0.8**
AST (IU/L)	747.7 ± 168.34	4416±642.05	**<0.0001**	**0.6**
ALT (IU/L)	923 ± 192.21	4763.5**±**744.58	**<0.0001**	**0.7**
Creatinine (mg/dl)	2.4**±** 0.7	1.2±0.35	**0.009**	**1.0**

DISCUSSION

Hepatitis A is frequently mild and asymptomatic in childhood and develops a mild self-limiting illness [14]. However, adults with HAV infection can develop more severe symptoms, leading to serious complications [8] and unusual pattern of hepatitis A, such as cholestatic hepatitis, relapsing hepatitis or prolonged course. Some hospital-based studies have suggested that the prevalence of anti-HAV antibodies among Indian adults has declined to <70% [15, 16]. Several studies have reported complications like prolonged hepatitis, relapse, hepatic failure, hematological abnormalities, etc in hepatitis A cases [17,18].Recent studies show that the rate of acute liver failure related to acute HAV infection has increased from 0.1-0.3% to 1.4% [8,12,19]. Studies have also reported that age ≥40 years, female gender, HBsAg positivity, peak PT (INR) ≥1.5, and peak total bilirubin were significant risk factors for severe complications in acute HAV infection [20]. This is the first

study of its kind in this region and in this study, among the 150 patients , two severe complications occurred in the hepatitis A patients : prolonged cholestasis (0.13%) and fulminant hepatic failure (0.02%) . Age >30 years, prothrombin time (INR) > 1.5, and serum creatinine levels were found to be risk factors for severe complications in acute hepatitis A infection.In this study, the clinical features of the three patient groups ie Acute, cholestatic and fulminant liver failure were compared with each other .The clinical risk factors for each of the complications of hepatitis A infection were also investigated by multivariate statistical analysis and old age was found to be a significant risk factor for the complications of hepatitis A infection and its severity. Studies have also confirmed that old age is a well-known risk factor for acute liver failure or mortality [8, 21]. Other studies by Rezende et al [22] have shown that older age, higher bilirubin levels, and female sex were predictors of poor prognosis of hospitalized hepatitis A patients. Studies conducted in Iran by Lankarani et al[23] have reported that most of the subjects in their study group belonged to the age group of <18 years old, which was significantly different from the older patients in western surveys and higher ALT levels and mild hepatic encephalopathy were associated with acute liver failure.

CONCLUSION

In conclusion, hepatitis A is symptomatic in adulthood which is occurring frequently and changing the epidemiologic pattern of the disease in this region. This changing pattern may also increase disease severity and incidence of complications of hepatitis A. So vaccination strategies against HAV in adult population, as well as children, and improved sanitation and health education will be of utmost need for the prevention of hepatitis A outbreak.

ACKNOWLEDGMENT

The first author thanks the Department of Science and Technology, New Delhi, India for INSPIRE Fellowship and supporting the research work.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest and also no financial interests relevant to the subject of the manuscript.

REFERENCES

1. Glikson ME, Galun R, Oren R, Kaspa T, Shouval D. Relapsing hepatitis A: review of 14 cases and literature survey. Medicine (Baltimore). 1992; 71:14–23.
2. Sjogren MH, Tanno H, Fay O, Sileoni S, Cohen BD, Burke DS, et al. Hepatitis A virus in stool during clinical relapse. Ann. Intern. Med. 1987; 106:221–226.
3. Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. Ann. Intern. Med. 1989; 110:838–839.
4. Cohen JI, Ticehurst JR, Purcell RH, Buckler WA, Baroudy BM. Complete nucleotide sequence of wild-type hepatitis A virus: Comparison with different strains of hepatitis A virus and other picornaviruses. J. Virol .1987; 61:50–59.
5. Robertson BH, Jansen RW, Khanna B, et al. Genetic relatedness of hepatitis A virus strains recovered from different geographical regions. J Gen Virol. 1992; 73: 1365–1377.
6. Costa-Mattioli M, Cristina J, Romero H, et al. Molecular evolution of hepatitis A virus: a new classification based on the complete VP1 protein. J Virol. 2002; 76:9516–9525.
7. Bell BP, Margolis HS, Alter MJ, Liang JT, Dienstag JL. Global epidemiology of hepatitis A: implications for control strategies, viral hepatitis and liver disease. International Medical Press, London, United Kingdom. p. 9–14.
8. Kim JI, Kim YS, Jung YK, et al. Factors influencing the severity of acute viral hepatitis A. Korean J Hepatol. 2010; 16:295-300.
9. O'Grady JG. Fulminant hepatitis in patients with chronic liver disease. J. Viral Hepatol. 2000;7 (Suppl. 1), 9–10.
10. Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann. Intern. Med. 1998; 128: 111–114.
11. Fujiwara K, Yokosuka O, Ehata T, Saisho H, Saotome N, Suzuki K, Okita K, Kiyosawa K, Omata M. Association between severity of type A hepatitis and nucleotide variations in the 50 non-translated region of hepatitis A virus RNA: strains from fulminant hepatitis have fewer nucleotide substitutions. Gut. 2002; 51: 82–88.
12. Jung YM, Park SJ, Kim JS, et al. Atypical manifestations of hepatitis A infection: a prospective, multicenter study in Korea. J Med Virol. 2010; 82:1318-1326.
13. Polso J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatol. 2005; 41:1179-1197.
14. Acharya SK, Batra Y, Bhatkal B, Ojha B, Kaur K, Hazari S, et al. Seroepidemiology of hepatitis A virus infection among school children in Delhi and north Indian patients with chronic liver disease: Implications for HAV vaccination. J Gastroenterol Hepatol. 2003; 18:822–7.
15. 15. Mall ML, Rai RR, Philip M, Naik G, Parekh P, Bhawnani SC, et al. Seroepidemiology of hepatitis A infection in India: Changing pattern. Indian J Gastroenterol. 2001; 20:132–5.
16. Jeong SH, Lee HS. Hepatitis A: clinical manifestations and management. Intervirol. 2010; 53:15-19.

17. Kamath SR, Sathiyasekaran M, Raja TE, Sudha L. Profile of viral hepatitis A in Chennai. Indian Pediatr. 2009; 46:642–3.
18. 18. Samanta T, Das AK, Ganguly S. Profile of hepatitis A infection with atypical manifestations in children. Indian J Gastroenterol. 2010; 29:31–3.
19. 19.Das K, Jain A, Gupta S, Kapoor S, Gupta RK, ChakravortyA,et al. The changing epidemiological pattern of hepatitis A in an urban population of India: Emergence of a trend similar to the European countries. Eur J Epidemiol. 2000; 16:507–10.
20. Yoo SH, Kim IH, Jang JW, Choi CH, Moon JC, Park JK, , et al. Clinical Features and Risk Factors for Severe Complications among Patients with Acute Hepatitis A Virus Infection in The Jeonbuk Province of Korea . Korean J Gastroenterol. 2014; Vol. 63 No. 1, 25-31.
21. Ajmera V, Xia G, Vaughan G, et al. Acute Liver Failure Study Group. What factors determine the severity of hepatitis A-related acute liver failure? J Viral Hepatol. 2011; 18:e167-e174.
22. Rezende G, Roque- Afonso AM, Samuel D, Gigou M, Nicand E, Ferre V, et al .Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatol.2003; 38(3):613–618.
23. Lankarani KB, Mahmoodi M, Honorary B, Nematollahi P, Zamiri N, Ghaffarpasand F. Determinants of poor outcome in patients with hepatitis A infection: a four-year retrospective study in Shiraz, Southern Iran. Arch Virol. 2013;