



CLINICAL AND ETIOPATHOLOGICAL CORRELATION OF ACUTE INFECTIVE HEPATITIS AND FULMINANT HEPATIC FAILURE IN PEDIATRIC PATIENTS

Paediatrics

Anubhav Choudhary*	Senior Resident, Department of Pediatrics, S.P. Medical College & P.B.M. Associated Group Hospitals, Bikaner, Rajasthan, India. *Corresponding Author
Sandeep Avasarala	Senior Medical Officer, Department of Medical, Health and Family Welfare, Ajmer, Rajasthan, India.
Gajanand Singh Tanwar	Professor, Department of Pediatrics, S.P. Medical College & P.B.M. Associated Group Hospitals, Bikaner Rajasthan, India.

ABSTRACT

INTRODUCTION- In India, infectious Hepatitis is one of the major health care burdens, with viral hepatitis being the most common culprit, followed by dengue, typhoid, and malarial hepatitis. Fulminant hepatitis manifests as a sudden abnormality in liver function enzymes in a child with no prior hepatic pathology.

AIMS AND OBJECTS- This study was aimed at identifying the various etiological factors and correlating clinical features of viral hepatitis, and fulminant liver failure.

MATERIALS AND METHODS- This observational study was conducted in the paediatrics in-patient department of S.P. Medical College & P.B.M. Associated Group of Hospitals, Bikaner (Rajasthan) over a period of one year. A total of 125 children with a clinical and lab-confirmed diagnosis of acute infective hepatitis were included. Data including clinical signs, symptoms, and laboratory parameters were obtained and analyzed.

RESULTS- Most commonly affected age group was between 5-10 years with the mean age being 7.1 ± 4.6 years. The most common etiology was hepatitis A ($n=39$), followed by hepatitis E ($n=24$) and mixed hepatitis A virus (HAV)/hepatitis E virus (HAE) infection ($n=20$). Other causative organisms were dengue virus ($n=16$), typhoid ($n=13$), malaria ($n=9$), and hepatitis B. The most common clinical symptoms were fever, jaundice, loss of appetite, and vomiting/nausea. There were some clinical features seen more commonly in case of infection with certain organisms. High frequency of diarrhoea, arthralgia, and thrombocytopenia was seen with HAV. Neurological, renal complications and high mortality were associated with HEV or HAV/HEV co-infection. While retroorbital pain and purpuric rash were exclusively with dengue, malarial hepatitis was strongly associated with pallor and altered sensorium.

CONCLUSION- Acute infective hepatitis is most commonly caused by HAV and HEV in Western Rajasthan. It is imperative to educate the masses regarding the prevention of common infections transmissible by infected drinking water, poor hand hygiene, improper waste disposal, and open defecation.

KEYWORDS

INTRODUCTION

The term Hepatitis refers to any inflammation or swelling of the liver. In India, infectious Hepatitis is one of the major health care burdens, with viral hepatitis being the most common culprit.^[1] Viral hepatitis is caused by 4 major hepatitis viruses, namely, A, B, C, and E. Hepatitis A virus (HAV), followed by hepatitis E virus (HEV) are the two most common variants of this virus to cause hepatitis in children.^[2] They can be isolated from the stool and blood of an infected child, and transmitted via the feco-oral route. Although HAV and HEV are often self-limiting, they are widely responsible for sporadic and epidemic outbreaks of acute viral hepatitis. However, in a small fraction of children, it may progress to acute or fulminant hepatic failure. Poor sanitation, overcrowding, malnutrition, and immunocompromised states make children prone to acquiring this infection.^[3]

Hepatitis B virus (HBV) and Hepatitis C virus (HCV), on the other hand, are predominantly transmitted via the parenteral route and rarely seen in children, unless perinatally transmitted via the mother. Both these viruses are known for causing chronic hepatitis, which may progress to liver cirrhosis and hepatocellular carcinoma.^[4] Other infective causes of hepatitis include dengue, malaria, and typhoid to name a few.^[5-7]

Fulminant hepatic failure is a highly specific and often fatal complication of hepatitis. It manifests as a sudden abnormality in liver function enzymes in a child with no prior hepatic pathology. It is associated with coagulopathy and altered sensorium secondary to hepatic encephalopathy. The most common cause of fulminant hepatic failure in children is viral hepatitis. Other rare causes are metabolic liver disease, seronegative hepatitis, sepsis, autoimmune hepatitis, and very rarely hemophagocytic lymphohistiocytosis. The mortality rates vary between 50%-70%.^[8]

It is always imperative to devise a rapid and precise aetiology for hepatitis in order to employ rapid treatment and prevent the development of morbid complications. Certain clinical features might provide a diagnostic clue for these etiological factors.

This study was aimed at identifying the various etiological factors and correlating clinical features of viral hepatitis, and fulminant liver failure.

MATERIALS AND METHODS

This observational study was conducted in the paediatrics in-patient department of S.P. Medical College & P.B.M. Associated Group of Hospitals, Bikaner (Rajasthan) over a period of one year from January 2021 to December 2021.

Inclusion Criteria

After obtaining due approval from the institutional ethics board and written informed consent from parents, children aged 6 months to 15 years with acute onset of jaundice, fever, vomiting/nausea, abdominal pain, anorexia, malaise, high color urine were recruited. Only children with lab-diagnosed hepatitis of infective origin diagnosed by positive viral markers like anti Hepatitis A or E IgM, or HbS Ag for HBV, Anti HCV, serology for typhoid, dengue, malaria were included.

Exclusion Criteria

Children having any prior history of liver disease or those with associated acute or chronic comorbidities were excluded. Children with chronic liver disease (suggested by a six-month or longer duration of illness) were excluded. Additionally, patients having non-infective hepatitis like metabolic, hematological, toxin, or drug (including antitubercular drugs) induced hepatitis were also excluded.

Infective hepatitis was diagnosed using serological tests, PCR techniques, and peripheral blood film analysis. Liver function tests, including serum bilirubin (total and direct), serum aspartate aminotransferase (AST) also known as serum glutamic oxaloacetic transaminase (SGOT), serum alanine aminotransferase (ALT) also known as serum glutamic pyruvic transaminase (SGPT) levels, serum gamma-glutamyl transferase (GGT), serum albumin, PT-INR, and blood glucose levels were measured. Detailed hematological and biochemical lab parameters were recorded for all the children.

A though general physical examination and systemic examination was done for all the cases. CNS symptoms were recorded. Children with features of altered sensorium decreased level of consciousness, seizures, or severe hypoglycemia were admitted to pediatric ICU and managed accordingly. For all such cases triage scoring, Glasgow coma scale score & encephalopathy grading were also carried out at baseline at repeated daily.

For diagnosing acute liver failure the 'Pediatric Acute Liver Failure study groups (PALFSG) consensus definition' was used. This definition includes any form of biochemical injury to the liver without any co-existing chronic liver disease, coagulopathy (not corrected by vitamin K), along with an International Normalized Ratio (INR) greater than 1.5 (with encephalopathy or greater than 2.0 (without encephalopathy) to be a case of acute liver failure.¹⁰ In children, the presence of significant coagulopathy without sepsis is a prominent feature of fulminant hepatic failure (FHF). FHF was further stratified into- hyper-acute (< 7 days), acute (8-28 days), and subacute (5 weeks to 12 weeks) on the basis of time taken for the development of encephalopathy after the onset of jaundice. Patient outcome was also recorded.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 19. Continuous and discrete variables were analyzed, a chi-square test was used and a p-value of <0.05 was taken to be statistically significant.

RESULTS

One hundred thirty children with acute infective hepatitis were identified. However, only 125 children were included in our study, while the remaining 14 were excluded due to the presence of chronic liver disease, lack of consent, or presence of an immunocompromised state. Seventy-four boys and 51 girls were included. Most commonly affected age group was between 5-10 years (n=64) (figure 1). The mean age of children was 7.1 ± 4.6 years.

The most common etiology was hepatitis A (n=39), followed by hepatitis E (n=24) and mixed HAV/HAE infection (n=20). Other causative organisms were dengue virus (n=16), typhoid (n=13), malaria (n=9), and hepatitis B (n=4) (table 1, figure 2).

The clinical symptoms included fever (n=113), jaundice (n=101), loss of appetite (n=93), vomiting/nausea (n=92), abdominal pain (n=89), anorexia (n=82), altered sensorium (n=28), gastrointestinal bleeding in the form of melena (n=19), and seizures (n=15). Other clinical features have been enlisted in table 2.

As far as physical findings were concerned 113 children had icterus, 77 had hepatomegaly, 41 had pallor, 37 had hepatic tenderness, 24 had peripheral edema, 18 had ascites, while 17 had splenomegaly (table 3). The gravest complications were Fulminant hepatitis seen in 37 children, and hepatic encephalopathy seen in 28 patients. Seven children had hyper-acute (< 7 days) FHF, 21 had acute (8-28 days), and 10 had subacute (5 weeks to 12 weeks) FHF. Other complications included decreased urine output (n=31), and septicemia (n=19). The overall survival rate of children affected with FHF was 27% (27 fatalities).

There were some clinical features seen more commonly in case of infection with certain organisms (table 4). Children infected with hepatitis A had a higher frequency of diarrhea (n=4), arthralgia (n=6), and thrombocytopenia (n=17). Neurological (seizures, altered sensorium, abnormal behavior), and renal complications were more common with hepatitis E or HAV/HEV co-infection. The rate of mortality was greatest with HAV/HEV co-infection (n=16). Retroorbital pain (n=7) and purpuric rash (n=6) were seen exclusively in children affected with dengue. Dengue was also strongly associated with headaches (n=16) and dark-colored urine (n=7). All the patients affected with typhoid had a fever. Malarial hepatitis was strongly associated with pallor (n=7) and altered sensorium (n=3).

There was a higher rate of mortality in children belonging to the rural background and between the ages of 5-10 years. Our observation that elevated levels of glutamic pyruvic transaminase (SGPT) >1000 U/L, hyperbilirubinemia (>10 mg/dl), and INR >1.5 were associated with a more severe course of illness and required a longer duration for recovery.

DISCUSSION

Acute infective hepatitis is a major public health problem in children, especially in a country like India with an abundance of rural and slum-dwelling populations belonging to poor socioeconomic status. Such children are prone to acquire a plethora of infections due to the absence of safe drinking water along with poor sanitation and personal hygiene.^[9]

In our study, there was a male preponderance with the male to female ratio being 1.4:1. These findings are comparable to those made by Behera et al.^[10] and Das et al.^[9] Just like these 2 studies, in our study as well the most commonly affected age group was between 5-10 years. A similar study done by Kamath et al. has also made similar observations with 61.6% of children belonging to 5-10-years of age group.^[11]

This study highlights the myriad causes of acute infective hepatitis and fulminant hepatic failure in children. Acute viral hepatitis A (31.2%) was the leading cause of fulminant hepatic failure in our study subjects followed by HEV infection (19.2%). Similar observations have been made by various authors in the past including Poddar et al., Behera et al., and Das et al.^[9,10,12] Co-infection of HAV/HEV was seen in 16% of patients, while 12.8% had dengue, 10.4% typhoid, 7.2% had malaria, and 3.2% had HBV. These findings signify the fact that a low threshold must be kept, and all children affected with acute hepatitis need to be screened for any co-existing infective aetiologies. Unlike adults where the most common cause of FHF is HEV, in the case of children we found HAV to be the leading cause of acute infective hepatitis and FHF.

The mortality in children with fulminant hepatic failure has been reported to range from 72%-94%. In our study, the rate of mortality of FHF was 72.9%. Similar observations have been made by Psacharopoulos et al.^[13], Saunders et al.^[15] who found 72% and 65% mortality rates in the case of FHF. Just like Psacharopoulos et al. we also observed that no clinical features encountered early in the course of the illness could be correlated with the survival of patients. However, a dramatically deranged laboratory profile was helpful in indicating the prognosis of individual cases.

In our study, we only found 4 cases of HBV. Due to mass vaccination drives and routine screening of blood donors, the incidence of acute hepatitis B has greatly reduced in the past 20 years. The various clinical presentations of infective hepatitis noted by us were fever (n=113), jaundice (n=101), loss of appetite (n=93), vomiting/nausea (n=92), abdominal pain (n=89), anorexia (n=82), altered sensorium (n=28), gastrointestinal bleeding in the form of melena (n=19), seizures (n=15), brown-colored urine (n=7), diarrhoea (n=5), and abnormal behaviour (n=3). These findings are comparable with the studies done by Das et al. and Parekh et al.^[9,15]

While the percentage of children presenting with icterus and fever in Das et al.'s study was 100% and 96.42% respectively, in Parekh et al.'s study 94% had jaundice and 82% had a fever.

Clinical examination of our cases revealed icterus to be the most consistent sign followed by hepatomegaly as well as hepatic tenderness. These findings are comparable with Girish et al.'s work.^[16] A few atypical clinical presentations were also noted by us including splenomegaly (n=24), ascites (n=18), and peripheral edema (n=17).

Biochemical parameters may also provide additional clues with context to the extent and severity of hepatic damage. The levels of total serum bilirubin and hepatic enzymes were raised in 120 (96%) patients in our study. Additionally, conjugated hyperbilirubinemia was also observed in almost all the cases (n=114; 91.2%). It was our observation that elevated levels of glutamic pyruvic transaminase (SGPT) >1000 U/L, hyperbilirubinemia (>10 mg/dl), and INR >1.5 were associated with a more severe course of illness and required a longer duration for recovery. The same observation has also been made by Das et al.

There were also some subtle differences in the clinical features depending upon the causative organism of acute hepatitis (Table 4). Children infected with hepatitis A had a higher frequency of diarrhea, arthralgia, and thrombocytopenia. On the contrary, neurological and renal complications were more common with hepatitis E or HAV/HEV

co-infection. Additionally, children affected with HEV or HAV/HEV co-infection had a graver course of illness. Out of the 37 children who developed hepatic encephalopathy, 11 were infected with HAV and 27 with HEV or HAV/HEV. All cases of FHF required PICU admission.

The rate of mortality was greatest with HAV/HEV co-infection. Retroorbital pain and purpuric rash were seen exclusively in children affected with dengue. Additionally, the frequency of headache, and dark-colored urine were seen more commonly in children affected with dengue. All the patients affected with typhoid had a fever. Malarial hepatitis was strongly associated with pallor and altered sensorium.

Table 1- Distribution of study subjects according to the causative organism

CAUSATIVE ORGANISM	NUMBER OF PATIENTS	PERCENTAGE
HAV	39	31.2%
HEV	24	19.2%
HAV/HEV	20	16%
Dengue virus	16	12.8%
Typhoid	13	10.4%
Malaria	9	7.2%
HBV	4	3.2%

Table 2- Distribution of study subjects according to clinical symptoms

SYMPTOM	NO.OF CHILDREN	PERCENTAGE
fever	113	90.4%
jaundice	101	80.8%
loss of appetite	93	74.4%
vomiting/nausea	92	73.6%
abdominal pain	89	71.2%
anorexia	82	65.5%
altered sensorium	28	22.4%
Headache	22	17.6%
gastrointestinal bleeding in the form of melena	19	15.2%
Skin rash	19	15.2%
Arthralgia	15	12%
seizures	15	12%
Pallor	7	5.6%
Brown colored urine	7	5.6%
Retro-orbital pain	7	5.6%
Diarrhoea	5	4%
Abnormal behaviour	3	2.4%

Table 3- Distribution of study subjects according to clinical signs

SYMPTOM	NO.OF CHILDREN	PERCENTAGE
Icterus	113	90.4%
Hepatomegaly	77	61.6%
Pallor	41	32.8%
Hepatic tenderness	37	29.6%
Peripheral edema	24	19.2%
Ascites	18	14.4%
Splenomegaly	17	13.6%

Table 4- Distribution of clinical features according to the causative organism

CAUSATIVE ORGANISM	DIFFERENTIATING CLINICAL FEATURE/LAB PARAMETER
HAV	diarrhea, arthralgia, and thrombocytopenia
HEV	Neurological and renal complications, higher mortality rate
HAV/HEV co-infection	Neurological and renal complications, higher mortality rate
Dengue	Retroorbital pain, purpuric rash, headache, and dark colored urine.
Typhoid	Fever, rash, hepatic tenderness
Malaria	Pallor and altered sensorium

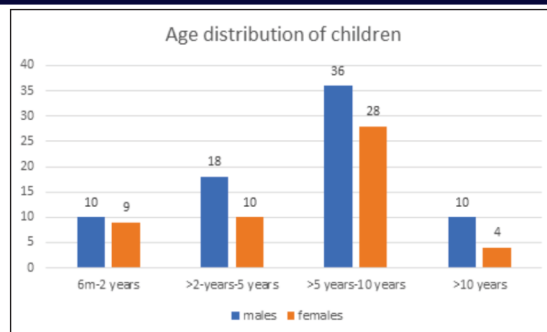


Figure 1- Age distribution of study participants

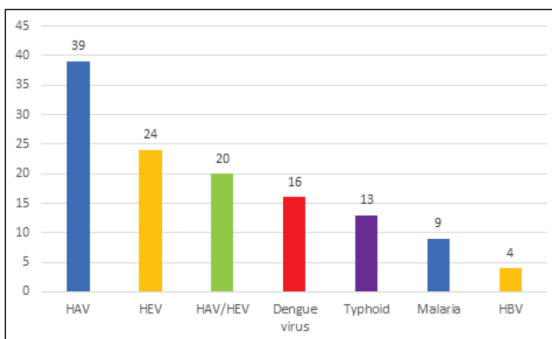


Figure 2- Distribution of study subjects according to causative agents

CONCLUSION

Acute infective hepatitis is most commonly caused by HAV and HEV in Western Rajasthan. Certain clinical features specific to each organism could help in differentiating the causative agents of acute infective hepatitis and fulminant hepatic failure which could help in early diagnosis and prompt treatment. It is imperative to educate the masses regarding the prevention of common infections transmissible by infected drinking water, poor hand hygiene, improper waste disposal, and open defecation. Government initiatives regarding vaccination against these infections are essential to halt the transmission and protect vulnerable children from the inadvertent morbidity and mortality associated with these infections.

REFERENCES

- Kc S, Sharma D, Poudyal N, Basnet BK. Acute Viral Hepatitis in Pediatric Age Groups. *JNMA J Nepal Med Assoc.* 2014;52(193):687-691.
- Owusu M, Bonney JK, Annan AA, Mawuli G, Okyere K, Mutocheluh M, et al. *PLoS One.* 2018;13(9):e0203699.
- Talati S, Khan SA, Javed N, Malik MI. Etiology, clinical presentation, and outcome of children with fulminant hepatic failure: Experience from a tertiary center in Pakistan. *Pak J Med Sci.* 2020;36(6):1252-1256.
- Kelly D. Viral hepatitis B and C in children. *JR Soc Med.* 2006;99(7):353-357.
- Karoli R, Fatima J, Chandra A, Singh G. Salmonella hepatitis: an uncommon complication of a common disease. *J Family Med Prim Care.* 2012;1(2):160-162.
- Shoukier H, Dham S, Bergasa NV, Kochar DK, Sirohi P, Abhishek K. Acute Hepatitis in Malaria. *Gastroenterol Hepatol (N Y).* 2006;2(1):35-38.
- Ishtiaq R, Imran A, Raza H, Anwar Q, Ishtiaq D, Jamil A, Ali QM, Khan R. Acute Hepatitis in Infections Caused by Dengue Virus in Southern Punjab, Pakistan. *Cureus.* 2018 Dec 28;10(12):e3788.
- Bhaduri BR, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis.* 1996;16(4):349-55.
- Das S, Deka A, Biswas T. Clinical Profile of Acute Viral Hepatitis in Children – In Southern Assam. *JMSCR* 2021;9:111-118.
- Behera MR, Patnaik L. Clinico-biochemical profile and etiology of acute viral hepatitis in hospitalized children: A study from Eastern India. *Indian J Child Health.* 2016; 3(4):317-320.
- Kamath SR, Sathiyasekaran M, Raja TE, Sudha L. Profile of viral hepatitis A in Chennai. *Indian Pediatr.* 2009;46(7):642-3.
- Poddar U, Thapa BR, Prasad A, Singh K. Changing Spectrum of Sporadic Acute Viral Hepatitis in Indian Children. *Journal of Tropical Pediatrics.* 2002 August: Vol. 48.
- Psacharopoulos HT, Mowat AP, Davies M, Portmann B, Silk DB, Williams R. Fulminant hepatic failure in childhood: an analysis of 31 cases. *Arch Dis Child.* 1980 Apr;55(4):252-8. doi: 10.1136/adc.55.4.252.
- Saunders S J, Hickman R, Macdonald R, Terblanche S J. The treatment of acute liver failure. In: Popper H, Schaffner F, eds. *Progress in liver disease.* Vol. 4. New York: Grune & Stratton, 1972: 333-44.
- Parekh Z, Modi R, Banker D. Clinical study of hepatitis in children with special reference to viral markers. *NHL J Med Sci.* 2013;2(1):23-7.
- Girish N, Sunil B., Ranganatha A. Devaranavadi A clinical study of viral hepatitis in children: a prospective hospital-based study. *International Journal of Contemporary Pediatrics.* 2018;5(2):563-568.