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Study on extrahepatic manifestations in patients with hepatitis A in a tertiary care hospital

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ABSTRACT

Background: Hepatitis A is a common self-limiting infection of the liver. In recent times, there is a change in the pattern of hepatitis A infection producing extrahepatic manifestations. **Aims and Objective:** Our aim of the study is to find the profile of extrahepatic manifestations of hepatitis A. The secondary objective is to find a correlation of liver function test values with extrahepatic manifestations. **Materials and Methods:** A retrospective study was conducted over 3 years. 169 seropositive school-going cases were presented with signs and symptoms of hepatitis A and were clinically assessed. **Results:** Among 169 immunoglobulin M (+)ve hepatitis A, 36% of patients (61 cases) presented with extrahepatic features. Among the 61 patients, 41 patients presented with aspartate transaminase (AST):alanine transaminase (ALT) >2:1 and 20 patients presented with AST:ALT <2:1. **Conclusion:** In recent times, there has been a changing pattern in the presentation of hepatitis A producing extrahepatic manifestations in the pediatric age group.

Key words: Extrahepatic manifestations; Hepatitis A; Liver function test

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INTRODUCTION

Hepatitis A is the most common acute, self-limiting course of liver infection, which is transmitted enterically by the picornavirus. Hepatitis A virus (HAV) belongs to the genus Hepatovirus in the family *Picornaviridae*. In the year 1947, there were two clinical forms of hepatitis – hepatitis A and hepatitis B.[1] In 1973 subsequently, the virus that was causing hepatitis A was identified by American virologist STEPHEN MARK FINESTONE.[2] HAV infection previously was commonly named as acute catarrhal jaundice and epidemic jaundice.

HAV is usually transmitted through the fecal-oral route. The patients suffering from the illness have had personal contact with an infected person. HAV usually spread before the index case has been recognized in childcare settings. Outbreaks are usually recognized only after childcare staff members develop symptoms.[3]

A study conducted among children found the age-related seroprevalence of HAV to be 50.3% in the age group of 6–10 years and 30.3% among 18 months to 6 years of age.[4] The HAV prevalence correlated strongly with the child's education and socioeconomic status. The HAV prevalence was found to be 97.2% in another study.[5] These findings were in agreement with the expected pattern of HAV seroprevalence in an area of high endemicity. Similar findings have been reported from other parts of the country as well.[6-8] About 90% of Indian children acquire protective antibodies against HAV by the age of 10 years. Similar patterns of endemicity have been found in other developing countries, with high seroprevalence of anti-HAV antibodies.[9]

In recent times due to different etiological factors, there has been a changing pattern that has been observed in the presentation of hepatitis A producing extrahepatic

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manifestations in the pediatric age group. This study has been done to find the profile of extrahepatic manifestations of hepatitis A and the correlation between the liver function test (LFT) and the extrahepatic clinical features.

Aims and objectives

Our aims and objectives of the study is to find the profile of extrahepatic manifestations of hepatitis A and the correlation of liver function test values with extrahepatic manifestations.

MATERIALS AND METHODS

This retrospective observational study was conducted over a period of 3 years (January 2021–December 2023) by collecting previous data from the Medical Record Department and taking seropositive patients admitted to the Department of Pediatrics of IQ City Medical College and Hospital, Durgapur, West Bengal. 169 children of 4–18 years of age diagnosed with viral hepatitis A (immunoglobulin [Ig]M positive) were included in this study.

Inclusion criteria

Hepatitis A IgM-positive patients were enrolled in this study.

Exclusion criteria

All patients suffering from other forms of hepatitis, such as hepatitis B, Wilson's disease, and pre-existing liver disease were excluded from the study.

The included patients were clinically assessed as per LFT and other routine blood investigations that were sent after hospitalization.

Clearance was collected from the Institutional Ethical Committee. Informed consent was obtained from all the parents of children included in the study. Age, sex, and age at the time of diagnosis were recorded. LFTs were done. According to the findings of the LFT, the patients were classified into two groups: First group had an aspartate transaminase (AST):alanine transaminase (ALT) ratio >2:1 and the second group of patients had an AST:ALT ratio <2:1. Data analysis was performed using Fisher's exact test on GraphPad 2×2 contingency table. $P<0.05$ was found statistically significant.

RESULTS

One-hundred sixty nine seropositive IgM +ve patients were enrolled in this study. The most common symptoms that patients presented with are moderate-to-high grade fever 91.4%, nausea and vomiting 85.5%, fatigue 70.1%, and 88.9% have mild-to-moderate abdominal pain. These patients were clinically examined. Upon examination, 97.7% of patients have jaundice. Some other common signs include 71.5% yellow discoloration of the sclera and on palpation, 69.6% of patients have tender hepatomegaly. 87% of patients have altered sleep patterns, 63.4% were presented with clay-colored stools and 55% have dark urination. The distribution of symptoms in IgM seropositive patients are listed in Figure 1.

Among the 169 seropositive patients 61 patients (36%) were presented with extrahepatic clinical features. Among these 61 patients,6 cases(9.8%)each had acute glomerulonephritis and pleural effusion, 15 cases(24.6%) were found to have thrombocytopenia, 8 cases(13.2%)had hemolysis, 7 cases (11.5%) were presented with ascites,4 cases (6.5%) with pancreatitis, 9 cases (14.8%) developed acute respiratory distress syndrome and 3 subjects(4.9%)each developed parotid and scrotal swelling. The distribution of Extrahepatic manifestations are listed in Figure 2.

Among these 61 patients who developed extrahepatic manifestations, 41 patients were found to have AST:ALT >2:1 whereas 20 patients with AST:ALT <2:1 ($P<0.5$). Patients with AST:ALT ratio >2:1 are significantly associated with the development of extrahepatic manifestations. The correlation between liver enzymes and extrahepatic features are shown in Table 1.

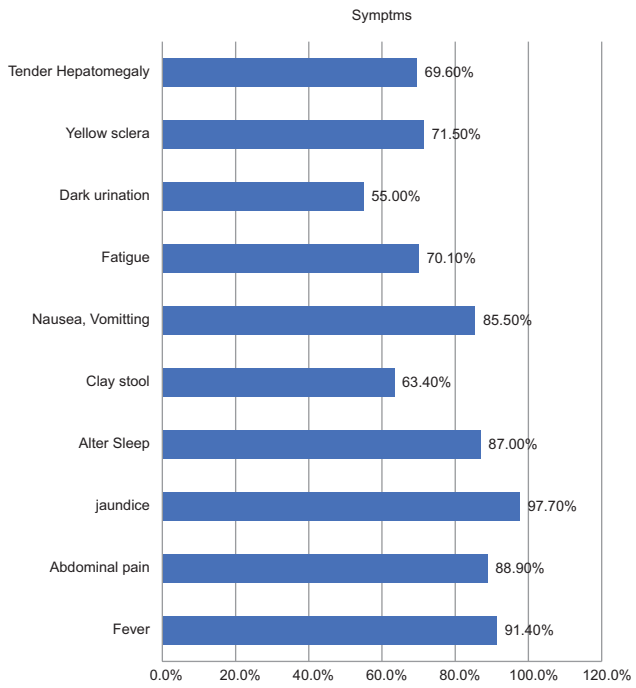

Figure 1: Distribution of symptoms in IgM seropositive patients

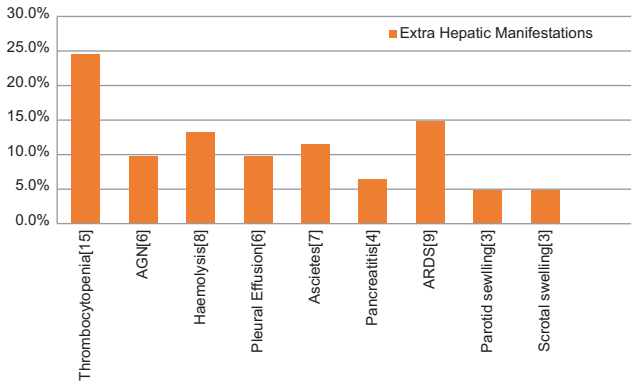

Figure 2: Distribution of Extra Hepatic Manifestations

Table 1: Correlation between liver enzymes and extrahepatic features

Extrahepatic manifestation	Present	Absent
AST:ALT >2:1	41	32
AST:ALT <2:1	20	76
	61	108

P=0.002

DISCUSSION

The clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. 30% of infected young children are symptomatic, with remarkably elevated serum AST and ALT levels. Atypical manifestations include relapsing hepatitis and prolonged cholestasis, and complicated cases with acute kidney injury have been reported. In this study, high fever, mild-to-moderate pain abdomen, and yellowish discoloration of the sclera were the triads of the most frequent symptoms that are presented among the maximum number of cases.

The incubation period of 2–7 weeks usually presents with typical symptoms which include fever, nausea, vomiting, abdominal discomfort, dark urine, and jaundice. Some patients show prolonged disease or relapsing disease lasting up to 6 months. The number of cases having elevated AST, ALT values, and AST:ALT >2:1 are more than cases having the same or low AST:ALT ratio level. Clinical illness and laboratory abnormalities recover within 2 months from the onset of illness along with decreasing levels of ALT and AST.

There have been rare cases of extrahepatic manifestation of hepatitis A that are found in other literature. These included autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia, pleural or pericardial effusion, acute reactive arthritis, acute pancreatitis, and neurologic complications, such as mononeuritis multiplex and Guillain–Barré syndrome. HAV remains an important cause of hepatitis outbreaks. Atypical features of hepatitis A include pleural effusion, ascites, acute glomerulonephritis, scrotal swelling, parotid swelling recurrent hepatitis, prolonged cholestasis, acute kidney injury, hemolytic anemia, and other extrahepatic manifestations. Other atypical manifestations include relapsing hepatitis, prolonged cholestasis, and complicated cases with acute kidney injury. Prolonged cholestatic hepatitis A was characterized by pruritus, fatigue, loose stools, and weight loss accompanying prolonged cholestasis. Acute kidney injury complicating non-fulminant hepatitis A was seen in 11%. Proposed mechanisms of renal damage include prerenal factors associated with anorexia, nausea, vomiting, diarrhea, and fever as well as nephrotoxic effects of hyperbilirubinemia, immune complex-mediated nephritis, interstitial nephritis, and rarely massive intravascular hemolysis.[10]

Elevated serum ALT is correlated with the inception of HAV and is present when individuals are symptomatic. ALT is often greater than AST, with levels 20–100 times the upper limit of normal.[11] Asymptomatic children with elevations in ALT and contact with an index case should be tested for HAV. Variability exists, as serum transaminases may normalize within approximately 3 weeks or remain elevated for several months. Serum bilirubin levels rise with the onset of jaundice, peak at approximately 10 mg/dL, and usually normalize within 4 weeks.[12-14] There are limited data in children showing elevated serum triglycerides at the onset of acute HAV. After recovery, serum triglycerides, cholesterol, and low-density lipoprotein decreased, while high-density lipoprotein increased in the same population.[15] In our study, seropositive hepatitis A children with AST:ALT ratio >2:1 significantly develop extrahepatic manifestations.

Limitations of the study

Limitations of our study were

1. It was retrospective observational study and the possibilities of the bias cannot be ruled out
2. Small sample size.

CONCLUSION

HAV infection continues to be one of the most frequently reported vaccine-preventable diseases, even with the most recent CDC and ACIP recommendations.[16] According to changes in HAV epidemiology, the disease burden of hepatitis A has increased in many regions because hepatitis A shows more severe clinical manifestations in children The outbreak of HAV remains a public health threat in the community.[17] According to this study, 36% of the total number of cases are presenting with extrahepatic clinical features. There has been scarcity of researches showing the relationship between AST ALT ratios and extrahepatic

features. With this study, it can be concluded that raised AST than ALT values play an important role in determining a relation with extrahepatic clinical features. Pediatricians should be aware of these extrahepatic clinical features so that timely screening can be done and management can be done expeditiously.

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REFERENCES

1. MacCallum FO. Homologous serum jaundice. Lancet. 1947;2:691.
2. Feinstone SM, Kapikian AZ and Purceli RH. Hepatitis A: Detection by immune electron microscopy of a virus like antigen associated with acute illness. Science. 1973;182(4116):1026-1028.
   https://doi.org/10.1126/science.182.4116.1026
3. Amit G, Monika G, Vikas G. A Study on Clinical and Biochemical Correlation in Hepatits A. (Paper Read in Pedicon); 2006.
4. Arankalle V, Mitra M and Bhave S. Changing epidemiology of hepatitis A virus in Indian children. Dove Med Press. 2014;4:7-13.
   https://doi.org/10.2147/VDT.S53324
5. Battegay M, Gust ID, Feinstone SM. Hepatitis A virus. In: Mandel JL, Bennett JE, editors. Principles and Practices of Infectious Diseases. New York: Churchill Livingstone; 1995. p. 1636-56.
6. Aggarwal R, Naik S, Yachha SK and Naik SR. Seroprevalence of antibodies to the hepatitis A virus among children in Northern India. Indian Paediatr. 1999;36(12):1248-1250.
7. Freidl GS, Sonder GJ, Bovée LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill. 2017;22(8):30468.
   https://doi.org/10.2807/1560-7917.ES.2017.22.8.30468
8. 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(7):822-827.
   https://doi.org/10.1046/j.1440-1746.2003.03051.x
9. Fix AD, Martin OS, Gallicchio L, Vial PA and Lagos R. Age-specific prevalence of antibodies to hepatitis A in Santiago, Chile: Risk factors and shift in age of infection among children and young adults. Am J Trop Med Hyg. 2002;66(5):628-632.
   https://doi.org/10.4269/ajtmh.2002.66.628
10. Kliegman RM, Stanton BM, Geme JS and Schor N. Nelson Text Book of Pediatrics. 20th ed. United States: W. B. Saunders Co.; 2015.
11. Harpaz R, McMahon BJ, Margolis HS, Shapiro CN, Havron D, Carpenter G, et al. Elimination of new chronic hepatitis B infections: Results of the Alaska immunization program. J Infect Dis. 2000;181(2):413-418.
   https://doi.org/10.1086/315259
12. Denson LA. Postnatal infections, part 1c: Other viral infections. In: Walker WA, editor. Pediatric Gastroenterology Disease: Pathophysiology, Diagnosis, Management. 4th ed. Hamilton, ON: BC Decker; 2004. p. 1170-8.
13. Al-Faleh FZ, Al-Jeffri M, Ramia S, Al-Rashed R, Arif M, Rezeig M, et al. Seroepidemiology of hepatitis B virus infection in Saudi children 8 years after a mass hepatitis B vaccination programme. J Infect. 1999;38:167-170.
   https://doi.org/10.1016/s0163-4453(99)90245-1
14. Ruff TA, Gertig DM, Otto BF, Gust ID, Sutanto A, Soewarso TI, et al. Lombok hepatitis B model immunization project: Toward universal infant hepatitis B immunization in Indonesia. J Infect Dis. 1995;171(2):290-296.
   https://doi.org/10.1093/infdis/171.2.290
15. Chunsuttiwat S, Biggs BA, Maynard J, Thamapalo S, Laoboripat S, Bovornsin S, et al. Integration of hepatitis B vaccination into the expanded programme on immunization in Chonburi and Chiangmai provinces, Thailand. Vaccine. 1997;15(6-7):769-774.
   https://doi.org/10.1016/s0264-410x(96)00226-5
16. CDC. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR07):1-23.
17. Rosenthal P. Hepatitis A: A preventable threat. J Pediatr Gastroenterol Nutr. 2002;35(5):595-596.
   https://doi.org/10.1097/00005176-200211000-00001

Authors Contributions:
AB- Definition of intellectual content, literature survey, prepared the first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **AD-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision, design of the study, statistical analysis and interpretation; **SA-** Review manuscript; review the manuscript, literature survey and preparation of figures, coordination, and manuscript revision.

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