

Atypical presentations of hepatitis A infection in children

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Abstract

Background Hepatitis A is the most common cause of acute viral hepatitis, with a typical simple, self-limiting course. But it is not free from complications. Atypical presentations, such as in the form of prolonged cholestasis, ascites, pleural effusion, relapsing hepatitis, or fulminant hepatic failure, pose challenges to disease management. Knowledge about varying presentations and identification of factors associated with atypical presentations will help to early diagnosis of atypical courses of disease.

Objective To describe various atypical clinical presentations, biochemical findings of hepatitis A infection, and possible related factors.

Methods Ninety-five children aged 1 to 18 years, diagnosed with hepatitis A infection, and admitted to the Department of Pediatric Gastroenterology & Nutrition, BSMMU, Dhaka, Bangladesh from January 2015 to May 2018 were studied retrospectively.

Results Atypical presentations were manifested in 19 (20%) out of 95 children with hepatitis A virus (HAV) infection. The mean age of atypical patients [6.32 (SD 3.45) years] was significantly lower than that of typical patients [8.22 (SD 3.58) years] ($P=0.0041$). The most common atypical manifestation was ascites (11/19), followed by hepatic encephalopathy (9/19), acute liver failure (7/19), thrombocytopenia (2/19), pleural effusion (2/19), and cholestasis (1/19). Children with atypical features had significantly higher international normalized ratio (INR) and serum bilirubin, as well as lower hemoglobin level than the typical group. Children of atypical group had significantly higher number of organomegaly and coagulopathy.

Conclusion Ascites, hepatic encephalopathy, acute liver failure, thrombocytopenia, pleural effusion, and prolonged cholestasis are common forms of atypical presentation. Younger age, organomegaly, higher bilirubin level, prolonged PT, and decreased hemoglobin level could be predictive of an atypical presentation of HAV in children. [Paediatr Indones. 2021;61:317-21 ; DOI: 10.14238/pi61.6.2021.317-21].

Keywords: hepatitis A; ascites; prolonged cholestasis; hepatic encephalopathy; atypical

Hepatitis A is one of the highly communicable diseases of mankind. It was first identified in 1973,¹ and remains one of the most common forms of acute viral hepatitis worldwide. This single-stranded non-enveloped RNA virus from the Picornaviridae family spreads via the feco-oral route and is mostly related to poor hygiene and unsanitary conditions in the community.² The highest incidence of hepatitis A infection has been reported in developing countries, including Africa, Central and South America, and South-East Asia. Bangladesh is considered to be highly endemic for hepatitis A infection, with 100% of children ≤ 6 years of age exposed to HAV.³ Though hepatitis A is a simple, acute, mostly asymptomatic and self-limiting disease, presentations may be diverse. It can range from asymptomatic infection to, rarely, fulminant hepatitis.^{4,5} Besides typical presentations, atypical forms of presentation include relapsing hepatitis, prolonged cholestasis, and extra-hepatic manifestations.⁶ The variety in manifestations adds

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some complexity to the simplicity of the disease. The clinical course of HAV infection is influenced mainly by age, as it is symptomatic in only 4-16% of children compared to 75-95% of adults.^{4,5} Awareness of atypical presentations and their detrimental effects may help provide consensus on disease prevention. Hepatitis A is a vaccine-preventable disease, and can be avoided with simple hygienic measures. Identification of factors related to atypical presentations should be helpful for early diagnosis of atypical course of the disease. As such, we aimed to describe atypical clinical presentations of HAV infection, biochemical findings, and possible risk factors related to atypical presentations.

Methods

Children with hepatitis A infection admitted to the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2015 to May 2018 were enrolled in the study retrospectively. Diagnosis of HAV infection was done on the basis of clinical findings (jaundice, fever, right upper abdominal pain, dark urine, anorexia, nausea/vomiting, itching, and tender hepatomegaly) as well as investigations [elevated alanine aminotransferase (ALT), international normalized ratio (INR), and total bilirubin] along with positive serum hepatitis A virus immunoglobulin M antibody (anti-HAV IgM detected by chemiluminescent assay, *Abbot Architect ci8200*, using HAVAb-IgM kit). Demographic data (age, gender) and other clinical presentations were documented from medical records. A total of 95 acute viral hepatitis patients aged 1 to 18 years were included in the study. Patients were divided into typical or atypical clinical presentation groups.

Atypical manifestations were defined as the presence of prolonged cholestatic hepatitis, relapsing hepatitis, and complications including coagulopathy, hepatic encephalopathy, acute liver failure, immune complex disorders, autoimmune disease, aplastic anemia, hemophagocytic syndrome, thrombocytopenia, acute renal failure, and pancreatitis. Cholestatic hepatitis was defined as direct bilirubin level higher than 50% of total bilirubin level with fever, itching, diarrhea, weight loss, total bilirubin level >10 mg/dL, and a clinical course lasting for at least 12 weeks. Extra-hepatic manifestations were

thrombocytopenia, leukopenia, rash, pleural or pericardial effusion, acute reactive arthritis and neurologic complications.⁷⁻⁹

The *Statistical Package for Social Science 20.0* (IBM SPSS; Chicago, Illinois) was used for statistical analysis. All results are presented as means with standard deviations (SD) or numbers with percentages. Chi-square test and Student's T-test were used for comparison of continuous variables between two groups, while Fisher's exact test was used for expected frequencies when the sample number was less than five in contingency tables. Correlation analyses were performed using Pearson's correlation coefficient. Results with P values <0.05 were considered to be statistically significant. This study was approved by the Ethics Committee of the Department of Pediatric Gastroenterology and Nutrition, BSMMU.

Results

A total of 95 patients were diagnosed with HAV infection. Among these, 51 (53.7%) were male and 44 (46.3%) were female. Atypical presentations were found in 19 (20%) of these cases. The most common atypical presentation was ascites (11 subjects), followed by hepatic encephalopathy (9), acute liver failure (ALF) (7), pleural effusion (2), thrombocytopenia (2), and prolonged cholestasis (1) (**Table 1**).

Mean age was significantly lower in the atypical group [6.32 (SD 3.45) years] than in the typical group [8.22 (SD 3.58) years]. Significantly higher percentages of organomegaly (P=0.001) and coagulopathy (P=0.035) were observed in the atypical compared to the typical group. Male sex, fever, jaundice, itching, and co-infection were more common in atypical patients,

Table 1. Clinical profiles of typical and atypical hepatitis A infection in children

Clinical presentation, n (%)	All patients (n=95)	Atypical variety (n=19)
Ascites	11 (11.6)	11
Prolonged cholestasis	1 (1.1)	1
Pleural effusion	2 (2.1)	2
Hepatic encephalopathy	9 (9.5)	9
Acute liver failure	7 (7.4)	7
Thrombocytopenia	2 (2.1)	2

but these differences were not statistically significant (Table 2). Among the laboratory findings, children with atypical features of hepatitis A had significantly higher international normalized ratio (INR) and serum bilirubin, as well as lower Hb% than children with typical manifestations. The ALT levels were not significantly different between the two groups (Table 3).

Discussion

Hepatitis A is endemic in developing countries and primarily affects children. Bangladesh is hyperendemic for hepatitis A, as 100% of children aged ≤ 6 years are exposed to hepatitis A. Although atypical manifestations have been reported in studies from different countries, there have been few reported from Bangladesh.¹⁰⁻¹² To our knowledge, this is the first study on atypical presentations of hepatitis A infection in Bangladeshi children. In our study, we retrospectively

evaluated 95 children infected with HAV, of whom 20% had atypical manifestations. This finding was similar to another study in India in which 22% of the study population had atypical presentations.¹³ The high rate of atypical presentations may have been due to our location in a tertiary care center, which may skew to more severe case presentations and admissions of symptomatic and referral cases. Nevertheless, this high rate is worthy of attention because hepatitis A is a preventable disease. Atypical presentations of hepatitis A have varying manifestations. Although the mechanisms of atypical manifestations remain unclear, past studies have suggested theories of immune complex depositions.^{14,15}

The most common atypical presentation in our study was ascites (11/19), similar to a previous study.¹² Ascites is believed to be due to venous or lymphatic obstruction due to liver involvement or reduction of oncotic pressure due to hypoalbuminemia during the course of disease.¹⁶ The second-most common presentation was hepatic encephalopathy (9/19),

Table 2. Comparison of demographic and clinical findings in children with typical and atypical hepatitis A

Parameters	Variety		P value
	Typical (n=76)	Atypical (n=19)	
Mean age (SD), years	8.22 (3.58)	6.32 (3.45)	0.041
Male/female gender, n (%)	37/39 (48.7/51.3)	14/5	0.051
Jaundice, n (%)	73 (96.1)	19	0.083
Abdominal pain, n (%)	29 (38.2)	6	0.597
Fever, n (%)	43 (56.6)	14	0.177
Anorexia, n (%)	18 (23.7)	4	0.809
Vomiting, n (%)	24 (31.6)	3	0.129
Organomegaly, n (%)	56 (73.7)	18	0.001
Itching, n (%)	3 (3.9)	1	0.820
Coagulopathy, n (%)	9 (11.8)	6	0.035
Co-infection, n (%)	12 (15.8)	4	0.607

Table 3. Comparison of laboratory findings in children with typical and atypical manifestations of hepatitis A

Parameters	Typical (n=76)	Atypical (n=19)	P value
Mean serum bilirubin level (SD), mg/dL	8.12 (6.78)	12.70 (8.95)	0.016
Mean ALT level (SD), IU/L	1,087.01 (954.40)	1,030.68 (909.86)	0.813
Mean INR (SD)	1.40 (0.40)	2.54 (2.23)	0.000
Mean Hb (SD), mg/dL	10.84 (1.72)	9.82 (1.64)	0.023

ALT=alanine aminotransferase, INR=international normalized ratio

followed by ALF (7/19 subjects). Among the 7 ALF patients, two died, 1 underwent liver transplantation and improved, and another 4 patients were cured. Nowadays, acute HAV infection is one of the most common causes of ALF in developing countries.¹⁷ An Indian study showed that ALF was quite common in HAV infection, and also the most common cause of ALF in Eastern India.¹⁸ Acute liver failure due to HAV infection is most likely secondary to an exaggerated immune response, and not due to cytopathic effects of the virus, as observed in an *in vitro* study.¹⁴ Multiple case reports show reactogenic phenomena like pleural effusion as an atypical presentation.^{15,19} Pleural effusion associated with hepatitis A infection usually occurs on the right side of the thorax,²⁰ but bilateral effusion may occur. The exact pathogenesis of pleural effusion is unclear, but inflammation of the liver, secondary to ascites or immune complex deposition, may be responsible.^{15,21} In our study, 2 of 19 patients had pleural effusion. Neurological, nephrological, and cardiovascular manifestations have been also documented, but none of our patients had these manifestations.²²⁻²⁴

In our study, thrombocytopenia, one of the hematological complications of acute hepatitis A, was observed in 2 out of 9 subjects. Immune thrombocytopenic purpura may be the only manifestation of acute hepatitis A according to a past study, without other manifestations such as jaundice, vomiting and abdominal pain.²⁴

A cholestatic phase of hepatitis A with persistently elevated bilirubin was seen in 1 patient. In patients with cholestasis, clinical symptoms, *i.e.* pruritis, persistent anorexia, dark urine, and coagulopathy, persisted throughout the course of illness. Cholestasis may be due to an inflammatory cytokine response. TNF- α and IL-1 inhibit MRP2, which is one of the proteins that play a role in bilirubin excretion.²⁵ Although statistically not significantly higher than in the typical patient group, multiple cases of co-infection with hepatitis E and/or salmonella were found in our study, possibly due to the common mode of disease transmission. In our study, children with atypical presentations were younger compared to those with typical disease course. This finding is similar to another study done on Lahore, Pakistan.²⁶ It may be due to higher number of the diseases at this age group as most of them are unaware about good sanitation, lack of

routine vaccination in our country and also endemicity. Regarding laboratory markers, higher INR and serum bilirubin, as well as lower Hb% were associated with children having atypical manifestations, similar to previous studies.^{26,27} Higher INR and serum bilirubin indicate more damage to hepatocytes.

A limitation of the study was that it was conducted solely in a tertiary care hospital among hospitalized children, so only symptomatic patients were included in the study. For this reason, our results may not accurately reflect the community. In addition, the sample size was small. Despite these limitations, hepatitis A infection should not be taken lightly, as atypical presentations may have detrimental effects. Disease prevention and cautious evaluation for early prediction of atypical presentation is necessary.

In conclusion, acute hepatitis A infection has different forms of atypical presentations which are not so uncommon. In our study, 20% patients presented with atypical manifestations, including ascites, hepatic encephalopathy, acute liver failure, thrombocytopenia, pleural effusion, and prolonged cholestasis. Younger age, organomegaly, higher bilirubin level, prolonged PT, and decreased hemoglobin level could be predictive of an atypical course of disease.

Further large-scale studies are needed to identify the true incidence of atypical features of HAV infection and related complications in Bangladeshi children. Our government should emphasize improvement of sanitation and hygiene practices for the prevention of hepatitis A infection. Also, our vaccination policy needs to be reviewed and updated.

Conflict of Interest

None declared.

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