

Hepatitis A in children: evaluation of atypical manifestations

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Abstract

Background Although hepatitis A infection is known as a benign, self-limited disease without chronicity, the rate of complications increases over time.

Objective To evaluate atypical manifestations of hepatitis A infection in children.

Methods A total of 130 children with hepatitis A infection were reviewed. Subjects' demographic and clinical characteristics, laboratory examinations, and clinical courses were evaluated retrospectively.

Results Twenty-one subjects had atypical manifestations of disease as follows: immune thrombocytopenic purpura (1 patient), pleural effusion (1), autoimmune hepatitis and hemolytic anemia (1), nephrotic syndrome (2), meningoencephalitis (2), autoimmune hepatitis (2), acalculous cholecystitis (3), relapsing hepatitis (4), and fulminant hepatitis (5). Only gender was significantly different, with males having more atypical manifestations than females ($P=0.03$). Mortality rate was 3% (3 patients with fulminant hepatitis and 1 with meningoencephalitis died in the intensive care unit).

Conclusion Although hepatitis A virus infection has a benign, self-limited course without chronicity, recognition of atypical cases which carry mortality risk is important. [Paediatr Indones. 2020;60:239-43 ; DOI: 10.14238/pi60.5.2020.239-43].

Keywords: complication; hepatitis A; infection; liver failure

Hepatitis A virus (HAV) is one of the most common infectious etiologies of acute hepatitis, which usually causes an asymptomatic infection in childhood. The symptoms and severity of infection vary according to age. Only 30% of children younger than 6 years of age with HAV infection develop symptoms which are typically non-specific, whereas 70% of infected adults have symptoms.^{1,2} Although it is known as a benign, self-limited disease without chronicity, the rate of atypical manifestations and complications increases over time in patients with HAV infection.³

The prevalence of atypical manifestations such as relapsing hepatitis, cholestasis, autoimmune hepatitis, hematological abnormalities, pleural effusion, pancreatitis, acute renal failure, and fulminant hepatic failure (FHF) varies from 1 to 30% (overall mean of 7%).²⁻⁶ There are a limited number of reports on pediatric HAV cases with atypical courses,⁴⁻¹⁸ thus, the aim of this study was to evaluate atypical manifestations of HAV infection in pediatric patients and determine the course of the disease.

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Submitted March 4, 2019. Accepted August 3, 2020.

Methods

A total of 130 children referred to the Division of Pediatric Gastroenterology, SBU Sisli Hamidiye Etfal Training and Research Hospital for HAV infection between 2003 and 2011 were evaluated retrospectively. Subjects underwent liver function tests [total bilirubin, direct bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)], coagulation tests [prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)], as well as serological tests for hepatitis A, B, and C virus by enzyme-linked immunosorbent assay (ELISA).

Patients with histories and signs of pre-existing chronic liver disease were excluded from the study. None of the subjects had a history of hepatotoxic drug ingestion. Parents provided written informed consent before procedures were done.

Relapsing hepatitis A was defined as a period of remission characterized by resolution of symptoms and normalization of biochemical parameters lasting 4 to 5 weeks followed by a second episode with clinical and biochemical manifestations demonstrated by PCR viral replication of HAV in serum or feces.⁴ Fulminant hepatic failure was defined if the patient had (i) no known chronic liver disease from birth to 18 years; (ii) biochemical evidence of acute liver injury; and (iii) coagulopathy not corrected by parenteral administration of vitamin K [having either INR between 1.5 and 2.0 (PT \geq 15 and $<$ 20 seconds) in the presence of hepatic encephalopathy (HE) or INR \geq 2 (PT \geq 20 seconds) with or without HE].^{19,20}

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 Statistical Software (Utah, U.S.A). Results are expressed as mean (SD). Statistical comparisons were made using unpaired Student's *t*-test and Chi-square test. A *P* value of $<$ 0.05 was considered to be statistically significant.

This retrospective study was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Results

None of the subjects had received hepatitis A vaccines. Their demographic and clinical characteristics are

shown in **Table 1**. The mean age of the 130 subjects was 6.1 (SD 4.1) years (range 1-16 years) and their male: female ratio was 1.03. Twenty-one of the 130 subjects [mean age: 6.47 (SD 3.2) years; M/F ratio 3.2] had atypical courses of disease (Table 2). Significantly more males than females had atypical courses of disease ($P=0.016$). Loss of consciousness, convulsion, nausea and vomiting, jaundice and hepatomegaly were significantly different between subjects with normal and atypical presentations (**Table 2**).

Table 1. Clinical and demographic characteristics of subjects

Characteristics	(N=130)
Mean age (SD), years	6.1 (4.1)
Male/female, n (ratio)	66/64 (1.03)
Symptoms, n (%)	
Nausea	26 (20)
Vomiting	87 (67)
Abdominal pain	56 (43)
Jaundice	83 (64)
Fever	26 (20)
Loss of appetite	52 (40)
Fatigue	52 (40)
Dark urine	32 (25)
Signs	
Hepatomegaly	84 (65)
Splenomegaly	3 (2.3)

The 21 subjects with atypical course of disease had the following conditions: immune thrombocytopenic purpura (ITP) (1 subject), pleural effusion (1), autoimmune hepatitis and hemolytic anemia (1), nephrotic syndrome (2), meningoencephalitis (2), autoimmune hepatitis (2), acalculous cholecystitis (3), relapsing hepatitis (4), and FHF (5). Two patients with relapsing hepatitis developed autoimmune hepatitis during their follow-up.

Conservative treatment was given to all subjects according to their diagnoses, such as corticosteroids for ITP and autoimmune hepatitis, anti-convulsants for meningoencephalitis, and treatment of hepatic coma in FHF. The mortality rate was 3% (3 FHF patients and 1 meningoencephalitis patient died in the intensive care unit).

Discussion

An increasing number of cases with atypical manifestations and complications of HAV infection in

Table 2. Clinical and demographic characteristics of subjects with atypical hepatitis A infection

Characteristics	Atypical hepatitis A infection (n=21)	Hepatitis A infection (n=109)	P value
Mean age (SD), years	6.47 (3.2)	6.2 (3.1)	0.71
Male/female ratio	16/5	50/59	0.016
Symptoms at admission, n			
Loss of consciousness	2	0	0.002
Convulsion	2	0	0.002
Nausea, vomiting	14	99	0.007
Jaundice	19	64	0.005
Cough	1	0	0.16
Abdominal pain	6	50	0.15
Clinical signs, n			
Hepatomegaly	7	77	0.002
Splenomegaly	2	1	0.06
Icterus	19	64	0.005
Petechiae	1	0	0.16
Laboratory findings of liver failure			
Mean ALT (SD), U/L (SD)	1.894 (1100)	1.978 (1336)	0.78
Mean AST (SD), U/L (SD)	2.165 (1587)	1.677 (1094)	0.08
Mean total bilirubin (SD), mg/dL	7.5 (5.3)	7.54 (5.85)	0.97
Mean direct bilirubin (SD), mg/dL	4.5 (3.2)	5.52 (4.75)	0.34
Mean total protein (SD), mg/dL	6.9 (0.8)	6.3 (1.4)	0.059
Mean albumin (SD), mg/dL	3.5 (0.5)	4.1 (3.4)	0.42
Mean prothrombin time (SD), sec	14.5 (8.3)	15.6 (4.74)	0.39
Mean fibrinogen (SD), mg/dL	210 (75)	270 (160)	0.09

Normal lab parameters: ALT (10-35 U/L); AST (10-40 U/L); total bilirubin (0.3-1.2 mg/dL); direct bilirubin (<0.3 mg/dL); total protein (6.2-8 mg/dL); albumin (4-5.9 mg/dL); prothrombin time (10-14 sec); fibrinogen (200-400 mg/dL). P<0.05 is statistically significant.

children⁴⁻¹⁸ and in adults^{4,17,21-26} have been reported. A previous study observed that atypical manifestations were more common in HAV infection than in hepatitis B infection (30% vs. 3%, respectively; P=0.00).⁶ The most common manifestation was prolonged cholestasis.⁵ We observed that FHF (5/21) was the most common atypical manifestation followed by relapsing hepatitis (4/21). Another study reported that children with atypical presentations were older than the patients without atypical presentations.⁵ Although we found no significant mean age difference between patients with atypical and normal presentations, we noted that significantly more males had atypical manifestations.

A study found that the rates of complications such as renal failure and cholestasis were significantly higher in adults >30 years of age than in children, but there was no significant difference in mortality according to age. Male patients predominated the group >30 years old in their study.¹⁷ We observed significant male predominance in the group of patients with atypical manifestations.

A previous study has mentioned that most of the the studies including adults did not document relapse by PCR testing of viral HAV clearance, thus, it is difficult to establish the exact prevalence of relapsing hepatitis.⁴ Another study reported the rate of relapsing hepatitis as 0.7%.¹⁷ However, it was the second most common atypical manifestation of HAV infection in our study, with 4/21 of our atypical subjects experiencing it (3% of all subjects). The proposed pathophysiologic mechanism for relapsing hepatitis is that hav was not completely eliminated in the 1st episode so it replicated, leading to a 2nd episode in patients with reduced immunity who may not have produced adequate antibody titers to clear the virus from the body.⁴ Our relapsing hepatitis patients were given conservative treatment and eventually complete clinical and biochemical resolution occurred.

A previous study observed that 38.7% of their patients had visible involvement of the gallbladder with >3 mm wall thickening, and 8% had acute acalculous cholecystitis. Thickening of the gallbladder wall was not significantly related to transaminase

levels, but was significantly associated with increased total and direct bilirubin levels.¹⁶ A study noted the following significant associations between the presence of any ultrasonographic finding and peak total bilirubin levels, the presence of ascites with peak ALT and AST levels, and the presence of biliary sludge.²⁶ In our study, 3/21 of the atypical cases had acalculous cholecystitis and no significant associations were found between laboratory findings according to presence/absence of acalculous cholecystitis, possibly because of the small number of cases.

Acute liver failure due to HAV infection is more common in adults than children and in patients with underlying chronic liver disease.^{e,4,27-29} The proposed pathophysiology is an exaggerated immune response, not the cytopathic effect of the virus in hepatocytes.⁴ A study reported that the most common cause of FHF was hepatitis A infection in children aged less than 4 years. Such FHF patients had higher degree of encephalopathy and INR >4, and those with higher serum bilirubin and lower AST had poor outcomes.¹⁵ Our FHF patients were also younger than 4 years.

The mortality rate was 3% in our study, mostly attributable to FHF as in the previous study.⁷ Three out of 5 of our FHF patients (3/5) died during hospitalization in the intensive care unit without liver transplantation. Another study reported that 57.1% of their patients with FHF showed spontaneous survival, 37.1% received liver transplants, and 14.3% died.³ Another study retrospectively reviewed 24 children with hepatitis A who showed evidence of liver failure in a single French urban pediatric liver transplantation center. They observed that encephalopathy occurred but resolved spontaneously in 7 children, and death or liver transplant were outcomes in 11 children (45.8%).¹⁰

The *Advisory Committee on Immunization Practices* (ACIP) has recommended hepatitis A vaccinations for all children during routine immunization, at the age of 12 to 23 months.³⁰ Preventive strategies targeting universal vaccination in children and active immunization of high-risk adults is important for prevention of community-wide outbreaks and complications of HAV infection.

In conclusion, primary health care providers should be aware of the potential atypical manifestations and complications of HAV infection and focus attention on childhood immunizations.

Conflict of Interest

None declared.

Funding Acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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