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Original Article

An Investigation on the Incidence and Clinical Importance of Atypical Complications in Children with Acute Hepatitis A Infection

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Abstract

Introduction: Atypical presentations in hepatitis A virus (HAV) infection are uncommonly encountered; nevertheless, they may lead to serious clinical complications. The present study reported the frequency of atypical presentations among children with acute HAV infection in south-east of Iran.

Materials and Methods: This prospective (cohort) study was conducted in the gastroenterology clinic of Amir-Al-Momenin Hospital (Zabol, Sistan and Baluchestan province, Iran). A total of 294 children with positive anti-HAV IgM test were enrolled during 2015-2018. They were prospectively monitored for the incidence of any atypical presentation.

Results: Out of 294 children, 152 (51.7%) were males, and the mean age was 7.3±3.5. Nausea and vomiting (41.8%) constituted the most frequent clinical presentations. Overall, atypical presentations were observed in 38 (12.8%). The atypical presentations included autoimmune hepatitis (AIH) (15, 5.1%), pancytopenia (11, 3.7%), non-immune hemolytic anemia (5, 1.7%), Wilson disease (3, 1%), prolonged cholestasis (3, 1%), and gallbladder hydrops (1, 0.3%). The mean level of alanine aminotransferase at diagnosis was significantly lower in patients with atypical presentations compared with those without such complications (801.28±986.61 vs. 1119.09±1109.98 IU/l, P=0.01). Patients with atypical manifestations also had significantly lower levels of total bilirubin (3.77±2.88 vs. 5.57±5.28 mg/dl, P=0.03) and direct bilirubin (2.03±2.06 vs. 2.91±3.20 mg/dl, P=0.04).

Conclusion: Atypical manifestations are relatively common among children with acute HAV infection and should be routinely screened. With timely and appropriate interventions, clinical outcomes may not be significantly different from patients with typical presentation.

Keywords: Hepatitis A, Complications, Pediatrics, Autoimmune Hepatitis

1. Introduction

Hepatitis A virus (HAV) is the etiology for a common viral infection affecting several people worldwide. HAV contains a single-strand RNA as its genetic material and is transmitted through oral routes. The clinical presentation of HAV infection ranges from asymptomatic to abrupt jaundice and hepatitis or chronic presentation with atypical complications. Young children usually follow an asymptomatic and self-limiting pattern while adults usually manifest jaundice of variable severities and durations. Fatigue, nausea, and dark urine are other common clinical presentations in acute HAV infection [1]. Although HAV infection is commonly recognized as an acute infectious disease, chronic illness may be observed in a ratio of patients. In patients with chronic

HAV infection, long-term atypical presentations are the most troublesome issue requiring prompt considerations [2].
The most serious long-term atypical complications of HAV have been recurrence of the disease, fulminant hepatitis, autoimmune hepatitis (AIH), cholestasis, hemolytic and plastic anemias, acute kidney failure, pericardial effusion, arthritis, and pancreatitis [3, 4]. AIH is a chronic liver disease characterized by the development of autoantibodies, hypergammaglobulinemia, and interface hepatitis in histological examination. Viral hepatitis can be a triggering factor for AIH in individuals with appropriate genetic signatures [5]. The overall prevalence of atypical manifestations in HAV infection has been reported as 7-14% [4, 6]; however, the incidence is variable based on the nature of the complication.
Our knowledge on atypical manifestations of HAV infection is merely limited to cases reports, and particularly, to few studies which have addressed the incidence of these complications among children both worldwide, and in Iran [4]. This lack of information can lead to inappropriate, unnecessary and often detrimental treatments in these patients. Therefore, this study aimed to address the incidence of atypical clinical presentations associated with acute HAV infection in children.

2. Materials and Methods

2.1 Patients

A total of 294 children appearing with acute HAV were prospectively (cohort) followed up. The patients were admitted to the gastroenterology clinic of Amir-Al-Momenin Hospital of Zabol, Iran during 2015-2018.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria were having icter and a positive result for anti-HAV IgM antibody test. Those children whose parents did not agree to participate were excluded. Also, the patients with evidences of other viral hepatitis infections (i.e. HBV, and HCV) were excluded.

2.3 Atypical Outcomes

The patients were prospectively watched over during a six-month period for the occurrence of any atypical presentation. These included AIH, pancytopenia (characterized with peripheral blood leukopenia, reticulocytopenia, and thrombocytopenia), Wilson disease (an inherited disease characterized with copper accumulation in the body organs, particularly liver), cholestasis (the obstruction of bile flow), gallstones, and hemolytic anemia.

2.4 Biochemical Parameters

After being diagnosed with acute HAV, blood samples were taken (10 ml) for determining hematological and biochemical parameters. Blood cell counts including white blood cell (WBC), red blood cell (RBC) and platelet count, as well as hemoglobin were recorded. Liver enzymes, namely alanine and aspartate aminotransferases (AST and ALT) were assessed both at the diagnosis and six months afterwards. Total and direct bilirubin, albumin, and total protein were also measured.

2.5 Statistical Analysis

The data was presented using descriptive statistics (SPSS 16). After checking for normality by Shapiro-Wilk test, Mann Whitney U test and independent samples student t-test were used to compare the intended variables between patients with typical and atypical presentations. For multiple group comparisons, either one-way ANOVA (parametric) or Kruskal-Wallis (non-parametric) test was used based on the distribution of the data. $P<0.05$ was assigned as the statistical significance level.

Ethical Approval

This study was conducted according to the Helsinki declaration (2013) and was

approved by the Ethics Committee of Zabol University of Medical Sciences (ethical code: Zbmu.1.REC.1396.65).

Informed Consent

The aim of the study was explained to the parents at first appointment, and informed consent was obtained from them.

3. Results

Out of 294 children, 152 (51.7%) were males and 142 (48.3%) were females. The mean age of the patients was 7.3±3.5 years (table 1). Nausea and vomiting (41.8%) constituted the most frequent clinical presentations (table 2).

Table 1. Clinical features of 294 children with acute hepatitis A infection

Parameters	Minimum	Maximum	Mean	Std. Deviation
Age (years)	0.5	27	7.3	3.5
Aspartate amino transferase (diagnosis) (IU/l)	24	5330	935.4	1069.1
Aspartate amino transferase (six months) (IU/l)	11	59	21.3	6.7
Alanine amino transferase (diagnosis) (IU/l)	16	5331	1121.5	1048.7
Alanine amino transferase (six months) (IU/l)	7.8	65	16.2	5.3
White blood cell count (ul)	2800	38000	7695.4	3326.1
Hemoglobin (g/dl)	7.1	19.2	11.9	1.5
Platelet (10^3/ul)	4.2	821	344.2	122.5
Albumin (g/dl)	3	8.1	4.4	0.8
Total Bilirubin (mg/dl)	0.1	22.4	4.6	4.2
Direct Bilirubin (mg/dl)	0.1	23.8	2.4	3.1
Total Protein (g/dl)	4	9.8	6.9	0.9

Table 2. Clinical presentation of 294 children with acute hepatitis A infection

Symptoms	n (%)
Nausea and vomiting	123 (41.8)
Dark urine	58 (19.7)
White stool	44 (14.9)
Icter	126 (42.8)
fever	101 (34.3)
Abdominal pain	89 (30.2)
Nil per os (NPO) intolerance	19 (6.4)
Itching	12 (4)
Coriza	14 (4.7)
Headache	6 (2)
Cough	4 (1.3)
diarrhea	8 (2.7)
Loss of appetite	29 (9.8)

The atypical presentations included AIH (15, 5.1%), pancytopenia (11, 3.7%), non-immune hemolytic anemia (5, 1.7%), Wilson disease (3, 1%), prolonged cholestasis (3, 1%), and gallbladder hydrops (1, 0.3%). There were no statistically significant differences comparing the mean age of patients with (10.2±11 years) and without (7.53±4.34 years) atypical presentations (P=0.63). The mean level of ALT at diagnosis was significantly lower in patients with atypical presentations compared with those without such complications (801.28±986.61 vs. 1119.09±1109.98 IU/l, P=0.01). Patients with atypical manifestations also had significantly lower baseline levels of total bilirubin (3.77±2.88 vs. 5.57±5.28 mg/dl,

P=0.03) and direct bilirubin (2.03±2.06 vs. 2.91±3.20 mg/dl, P=0.04). Regarding other variables, no significant differences were observed between those with or without atypical presentations (Table 3).

Table 4 describes the mean values of age and biochemical and hematological variables in groups of patients with each specific atypical presentation. The levels of AST, ALT, as well as WBC and platelet count significantly differed among patients with different HAV-associated atypical manifestations. Other variables showed no statistically significant differences among these groups.

Table 3. Comparison of laboratory parameters between HAV-infected children with or without atypical presentations

Parameters	With atypical presentations	Without atypical presentations	P value
Age (years)	10.23±11	7.53±4.34	0.63
AST (IU/l)	687.69±841.29	881.12±1016.1	0.15*
ALT (IU/l)	801.28±986.61	1119.09±1109.98	0.01*
Albumin (g/dl)	4.28±0.98	4.37±0.84	0.68
Total protein (g/dl)	7.52±1.29	7.60±1.77	0.81
Total bilirubin (mg/dl)	3.77±2.88	5.57±5.28	0.03*
Direct bilirubin (mg/dl)	2.03±2.06	2.91±3.20	0.04*
WBC (10^3/ul)	6.69±3.96	7.65±3.29	0.14
Hemoglobin (g/dl)	11.4±2.46	11.87±1.78	0.20
Platelet (10^3/ul)	263.37±182.96	313.21±150.36	0.09

*; Mann-Whitney U test. Abbreviations: AST; aspartate aminotransferase, ALT; alanine aminotransferase, WBC; white blood cell count.

Table 4. Laboratory parameters in children with acute HAV infection with typical and atypical presentations

Parameters	Atypical presentations of acute HAV infection						
	Typical	AIH† (N=15)	Pancytopenia (N=11)	NIHA (N=5)	Cholestasis (N=3)	WD (N=3)	P
Age (years)	7.4 ± 4.3	12.6 ± 4.4	6.5± 3.5	5.4±3.9	3.8±2	10.3±5	0.056
AST (IU/l)	880.7 ± 1010.5	623.05 ± 856.1	1365.9±10002.8	566.8 ±484.1	370.6±254.2	232 ±126.4	0.06*
ALT (IU/l)	1115.7±1104.3	760.9±1044.3	1365±1110.2	864.8±892.2	463.3±156.8	271.6±183.1	0.06*
WBC (10^3/ul)	7.6±3.2	7.3±3.7	2.6±1.1	6.4±3.1	7.7±1.3	6.4±4.9	0.001
Hemoglobin (g/dl)	11.8±1.7	11.8±2.7	9.3±0.8	10.8±1.5	11.3±0.8	12.2±3.2	0.056
Platelet (10^3/ul)	314.5±149.8	306±168.2	49.8±23	225.5±163.6	429.5±334.4	331.5±283.5	0.001
Alb (g/dl)	4.3±0.8	4.2±0.6	4.4±0.5	3.9±0.2	3.51.2	3.8±0.7	0.28
TB (mg/dl)	5.6±5.2	3.4±2.7	3.7±2.2	4.3±2.1	6.4±2.3	1.3±0.7	0.38
DB (mg/dl)	2.9±3.1	2±1.9	2.9±2.2	2.7±3.7	3.2±2.4	0.5±0.4	0.81
TP (g/dl)	7.5 ±1.7	7.7±1	6.3±3.2	9.3±0.2	5.6±4.9	6.4±0.7	0.16

*; Kruskal-Wallis test. †; Abbreviation: IBD: inflammatory bowel disease, AIH; autoimmune hepatitis, NIHA; non-immune hemolytic anemia, WD; Wilson disease, AST; aspartate aminotransferase, ALT; alanine aminotransferase, WBC; white blood cell count, Alb; albumin, TB; total bilirubin, DB; direct bilirubin, TP; total protein

The patients with cholestasis were successfully managed by the administration of UDCA (15 mg/kg/day). The patients with AIH were managed by prednisolone (2 mg/kg) daily. Those with Wilson disease were administrated with penicillamine. The patients with hemolytic anemia and pancytopenia were also managed by transfusion of blood products. These patients recovered spontaneously and did not require immunosuppressive therapies. There were no deaths or disease recurrences

among patients who presented with atypical manifestations.

4. Discussion

Atypical presentations in patients with acute HAV infection may deviate the clinical course of this infection from a benign self-limiting disease to a life-threatening situation. In the present study, the incidence of atypical complications in acute HAV infection was screened among 294 children. The observed atypical presentations included AIH (5.1%), pancytopenia (3.7%), hemolysis (1.7%), Wilson disease (1%), cholestasis (1%) and hydrops (0.3%). The mean level of ALT at diagnosis was significantly lower in patients with atypical presentations compared with those without such complications (801.28±986.61 vs. 1119.09±1109.98 IU/l, P=0.01). Patients with atypical manifestations also had significantly lower levels of total bilirubin (3.77±2.88 vs. 5.57±5.28 mg/dl, P=0.03) and direct bilirubin (2.03±2.06 vs. 2.91±3.20 mg/dl, P=0.04) at diagnosis. However, no significant differences were observed between those with or without atypical presentations regarding age and baseline levels of AST, albumin, total protein, WBC, hemoglobin, and platelet count.

AIH has been reported alongside with HAV infection merely as case reports [7-14]. The development of AIH over HAV course may result in persistent positivity for anti-HAV IgM antibodies even after 18 months to four years following the diagnosis [11, 15]. In a mutual interaction, it has been noted that HAV infection itself may trigger autoimmunity against hepatocytes [7, 11, 16-18]. In fact, HAV and AIH may be indifferentiable during initial phases [19], and chronic HAV infections are suggested to be further scrutinized for the evidences of AIH [15]. Persistent elevated liver enzymes following treatment of HAV infection may indicate the development of AIH [9]. If left untreated or undiagnosed, AIH may progress to liver failure, and therefore, the identification of concurrent AIH in the context of acute viral hepatitis is of crucial importance [2].

In the present study, 3 out of 294 children with acute HAV infection were diagnosed with Wilson disease during the course of the disease. The diagnosis of Wilson disease may be difficult from AIH in the context of viral hepatitis [20]. However, in the present study, patients with Wilson disease did not show any significant difference in laboratory findings at presentations. Wilson disease is a rare congenital defect of copper transportation and is associated with direct cytotoxicity to hepatocytes due to copper overload [21]. Furthermore, 11 of our patients developed pancytopenia. Pancytopenia is among relatively common hematologic manifestations of HAV infection. Pancytopenia in children with acute hepatitis is usually transient requiring no serious intervention [22]. In the 11 patients identified in our study, all were recovered spontaneously and were managed by transfusion of blood products. Nevertheless, this condition also may be progressive leading to even death secondary to comorbidities [23]. Pancytopenia is usually a part of hepatitis-associated aplastic anemia which may be seen several weeks after hepatitis diagnosis [24-26]. The pathogenesis is supposed to be related to immune dysregulation triggered by the virus [27]. Other causes of pancytopenia in patients with acute viral hepatis may be intensive splenomegaly [28] and hemophagocytic syndrome [29].

In the present study, non-immune hemolytic anemia was observed in 5 out of 294 patients. Although hemolysis is a relatively common atypical presentation in acute HAV infection [30] and other viral causes of hepatitis [31, 32], but this has been associated with autoimmune hemolytic anemia as evidenced by several case reports in this context [8, 33-35]. This phenomenon has been further suggested to be associated with AIH [31, 36]. Neither of our patients represented positive coombs tests which

ruled out the autoimmune nature of the hemolysis. Instead, schistocytes along with thrombocytopenia were seen in peripheral blood smear reviews indicating a possible microangiopathic hemolytic anemia.

Cholestasis may be encountered in some children with acute HAV infection [37], which may prolong hospital stay [38]. Cholestatic hepatitis has been reported in 2.5-6.1% of HAV-infected children [6, 39]. Among adults with acute HAV infection, cholestasis was noted as 2-6.8% [1, 40-42]. The administration of herbal drugs has been noted as a risk factor for cholestasis in children with HAV infection [43]. Other risk factors have been noted as concurrent Dubin-Johnson syndrome [44], INR >1.5 [42], and concomitant HBV infection [41, 45]. Cholestasis may also indicate a relapse of HAV infection [33], therefore, these patients should be carefully watched.

From limitations of this study was the low number of patients with some specific atypical presentations such as Wilson disease and cholestasis (each with n=3), and hemolytic anemia (n=5), which limited the power of study. Besides HBV and HCV, we did not test for other viral causes of hepatitis; however, because very low frequencies of these types in our region, and in clinical examinations, we tried to rule out any other underlying hepatic diseases. Researchers are suggested to assess the incidence and clinical course of these atypical manifestations in other populations.

5. Conclusion

Atypical manifestations are relatively common among children with acute HAV infection. Pediatricians should be aware of these complications and take appropriate diagnostic and therapeutic measures. Although some presentations such as pancytopenia and hemolytic anemia may be resolved spontaneously, attention ought to be paid to prolonged situations.

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Conflict of interest

The authors declare no conflict of interest.

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