Atypical clinical manifestations of hepatitis a among children aged 1-16 years in South-Eastern Region of Turkey

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Hepatitis A virus (HAV) infection has several atypical manifestations, including fulminant hepatitis, relapsing hepatitis, prolonged cholestasis and extra-hepatic manifestations. In this study, we aimed to describe the characteristics and outcomes of the pediatric patients with atypical manifestations of HAV infection. Four hundred twelve children with symptomatic hepatitis A infection admitted to Gaziantep Children's Hospital Department of Pediatric Infectious Disease between August 2011 and January 2013 were analyzed retrospectively. Atypical presentations were present in 53 (12.8%) children of 412 children with HAV infection. Patients with atypical presentations (8.3±3.7 years) were older than patients with typical presentations (5.9±3.1 years) (p=0.001). Children with atypical features of hepatitis A statistically had higher initial and peak values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), serum total and direct bilirubin than typical manifested group.

We can conclude that older age is the major risk factor for atypical presentation of HAV infections. Higher initial and peak levels of AST, ALT, INR, total and direct bilirubin could predict the atypical manifestation.

Key words: hepatitis A, atypical, child.

Hepatitis A is generally an acute, self-limiting liver infection transmitted through the fecal-oral route by a positive-strand RNA virus, the hepatitis A virus (HAV), which causes 10 million infections worldwide each year[1,2]. The clinical spectrum ranges from mostly asymptomatic infection to rarely fulminant hepatitis[3,4]. In addition to fulminant hepatitis, hepatitis A has several atypical manifestations, including relapsing hepatitis, prolonged cholestasis and extra-hepatic manifestations[5]. Age is the major factor that influences the clinical course of the primary HAV infection; it is symptomatic in only 4%–16% of children compared to 75%–95% of adults[3,4]. Furthermore, high peak value of serum bilirubin was associated with the atypical manifestation[4].

Although a highly effective and safe vaccine for HAV was implemented since November 2012, HAV is still an important etiology of acute viral hepatitis in Turkey. HAV infection prevalence has a strong relationship with social, economical and environmental factors. The prevalence rate of hepatitis A for Turkey has been reported as 64.4% and it was more than 90% for south-eastern region of Turkey[6].

In this study, we aimed to describe the characteristics and outcomes of the pediatric patients diagnosed with HAV infection and relationship between atypical manifestations and clinical, laboratory findings in the south-eastern region of Turkey.

Material and Methods

Four hundred twelve children with symptomatic hepatitis A infection admitted to Gaziantep Children's Hospital Department of Pediatric Infectious Diseases between August 2011 and

Table I. Profile of Hepatitis A Infection in Children with Atypical Manifestations.

Clinical presentation	All patients (n= 412) %	Patients with atypical manifestations (n= 53) %
Prolonged cholestasis (n=21)	5.1	39.6
Complicated hepatitis (n=18)	4.3	34
Fulminant hepatitis (n=3)	0.7	5.6
Extra-hepatic complication (n=15)	3.6	28.4
Pleural effusion (n=5)	1.2	9.4
Thrombocytopenia (n=5)	1.2	9.4
Leukopenia (n=2)	0.6	3.9
Rash (n=1)	0.2	1.9
Arthritis (n=1)	0.2	1.9
White matter lesion (n=1)	0.2	1.9
Relapsing hepatitis (n=14)	3.4	26.4
Total (n=53)	12.8	100

January 2013 were analyzed retrospectively. Diagnosis of HAV infection was made by positive serum hepatitis A virus immunoglobulin M antibody (anti-HAV IgM) (Chemiluminescent assay, Abbott Architect ci8200, using HAVAb-IgM kit).

Demographic data (age, gender), clinical findings (fever, fatigue, jaundice, dark urine, nausea/vomiting, diarrhea, itching, headache, abdominal pain) and laboratory findings [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), international normalized ratio (INR), total bilirubin, direct bilirubin] of patients were documented.

Atypical manifestations were defined as relapsing hepatitis, prolonged cholestasis, complicated cases with fulminant hepatitis and extra-hepatic manifestations. Relapsing hepatitis A was characterized by a biphasic peak of serum aminotransferase elevation with 1 to 4 month intervals between the first and second peak with ongoing anti-HAV IgM positivity[5]. Prolonged cholestasis was defined as direct bilirubin level higher than 50% of

Table II. Comparison of Demographic and Clinical Findings in Children with Typical and Atypical Clinical Manifestations of Hepatitis A.

Parameters	Typical manifestations n (%)	Atypical manifestations n (%)	P
Age (year) (mean±SD)	5.9±3.1	8.3±3.7	0.001
Gender (Male/Female)	161/198	21/32	0.47
Fever	163 (45.4)	30 (56.6)	0.13
Fatigue	138 (38.4)	31 (58.4)	0.006
Jaundice	279 (77,7)	49 (92.5)	0.01
Dark urine	197 (54.9)	41 (77.4)	0.004
Nausea/Vomiting	178 (49.6)	37 (69.8)	0.006
Diarrhea	94 (26.2)	18 (34)	0.23
Itching	137 (38.2)	25 (47.2)	0.21
Headache	99 (27.6)	14 (26.4)	0.81
Abdominal pain	139 (38.7)	28 (52.8)	0.51
Total	359 (100)	53 (100)	

SD: Standard deviation.

Table III. Comparison of Laboratory Findings in Children with Typical and Atypical Manifestation of Hepatitis A

Parameters	Typical manifestations (mean±SD) (Initial / peak value)	Atypical manifestations (mean±SD) (Initial / peak value)	P
ALT (IU/L)	1605±818/2028±945	1914±628/2394±882	0.003/0.008
AST (IU/L)	1430±752/1914±911	1751±616/2198±811	0.009/0.03
Total bilirubin (mg/dL)	5.5±2.5/6.3±3.23	7.3±2.9/9.7±4.9	0.03/0.001
Direct bilirubin (mg/dL)	2.9±1.9/3.8±2.2	5.0±2.8/5.8±3.1	0.001/0.001
GGT (IU/L)	138±99/148±105	149±95/154.1±128	0.4/0.7
ALP (IU/L)	196±61/215±81	179±99/220±140	0.2/0.6
INR	1.09±0.43/1.13±0.4	1.32±0.65/1.45±0.8	0.001/0.001

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transpeptidase, ALP: Alkaline phosphatase, INR: International normalized ratio, SD: Standard deviation.

total bilirubin level with fever, itching, diarrhea, weight loss and total bilirubin level higher than 10 mg/dl and a clinical course lasting for at least 12 weeks[7,8]. Extra-hepatic manifestations included thrombocytopenia, leukopenia, rash, pleural or pericardial effusion, acute reactive arthritis and neurologic complications[5].

Statistical analysis was performed with the Statistical Package for the Social Sciences version 17.0 (SPSS, Microsoft Inc. Chicago, USA). All results were presented as means with standard deviations (SD) or number of instances (percent). Student's t-test was used for comparison of continuous variables between two groups. Fisher's Exact Test was used for expected frequencies less than five in contingency tables. Correlation analyses were performed using Pearson's correlation coefficient. P values <0.05 were considered statistically significant.

The protocol of this study was approved by the Ethics Committees of Gaziantep University, Faculty of Medicine, and the study was conducted in accordance with the principles

Table IV. Comparison of Demographic and Clinical Findings in Children with Atypical Clinical [prolonged cholestasis, relapsing hepatitis and complicated hepatitis (hepatic and extra-hepatic)] Manifestations of Hepatitis A

Parameters	Prolonged cholestasis n (%)	Relapsing hepatitis n (%)	Complicated hepatitis (Hepatic and extra-hepatic) n (%)	P
Age (year) (mean±SD)	11.0±2.8	7.6±2.6	5.6±3.4	0.001
Gender (Male/ Female)	9/12	4/10	8/10	0.61
Jaundice	21 (100)	14 (100)	14 (77.8)	0.02
Dark urine	20 (95.2)	10 (71.4)	11 (61.1)	0.03
Itching	15 (71.4)	4 (28.6)	6 (33.3)	0.01
Fever	13 (61.9)	6 (42.9)	11 (61.1)	0.48
Fatigue	12 (57.1)	7 (50)	12 (66.7)	0.62
Nausea/Vomiting	16 (76.2)	10 (71.4)	11 (61.1)	0.58
Diarrhea	8 (38.1)	5 (35.7)	5 (27.8)	0.78
Headache	7 (33.3)	2 (14.39	5 (27.8)	0.65
Abdominal pain	15 (71.4)	5 (35.7)	8 (44.4)	0.26

SD: Standard deviation.

of the Declaration of Helsinki.

Results

Totally 412 patient were diagnosed as HAV infection. Among these, 182 (44.2%) were male and 230 (55.8%) were female. The mean age of the patients was 6.25±3.28 (1-16.5) years. Atypical presentations were present in 53 (12.8%) of these cases. Prolonged cholestasis [21 patients (39.6%)] was the most common atypical presentation (Table I). Fourteen patients had relapsing hepatitis (3.4%) and in 3 patients fulminant hepatitis occurred (0.7%). In 15 patients, extra-hepatic complications were determined (3.6%) (Pleural effusion in 5 patients, thrombocytopenia in 5 patients, leukopenia in 2 patients, rash in one patient, arthritis in one patient and white matter lesion in one patient) (Table I). The mean time of relapse was 8.1±2.3 weeks in children with relapsing hepatitis. In children with prolonged cholestasis, the mean period of cholestasis was 12.3±0.9 weeks.

Patients with atypical presentations (8.3±3.7 years) were older than patients with typical presentations (5.9±3.1 years) (r=0.27, p=0.001). Fatigue, nausea/vomiting, jaundice and dark urine were statistically more common in patients with atypical manifestation (Table II). Fever, diarrhea, itching and abdominal pain were more common in patients with atypical presentations but these differences were not statistically significant (Table II).

Among the biochemical markers, children with atypical features of hepatitis A statistically had higher initial and peak values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), serum total and direct bilirubin than children with typical manifestations (Table III). In terms of gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels, there were no statistically significant differences between two groups (Table III).

In the comparison of demographic and clinical findings of children with atypical manifestations, jaundice, dark urine and itching were statistically found to be more frequent in children with prolonged cholestasis than children with relapsing hepatitis and complicated hepatitis. Furthermore, children with prolonged cholestasis were older than other two groups (p=0.001) (Table IV).

Laboratory investigations showed that children with prolonged cholestasis had statistically higher initial and peak GGT, ALP, total and direct bilirubin levels than children with

Table V. Comparison of Laboratory Findings in Children with Atypical Clinical [prolonged cholestasis, relapsing hepatitis and complicated hepatitis (hepatic and extra-hepatic)] Manifestations of Hepatitis A

Parameters	Prolonged cholestasis (mean±SD) (Initial / peak value)	Relapsing hepatitis (mean±SD) (Initial / peak value)	Complicated hepatitis (Hepatic and extra-hepatic) (mean±SD) (Initial / peak value)	P
ALT (IU/L)	1901±709/2411±930	1711±467/2189±739	2088±619/2534±944	0.24/0.55
AST (IU/L)	1739±681/2224±817	1610±457/2025±658	1873±648/2304±925	0.49/0.62
Total bilirubin (mg/dL)	9±2.3/12.7±2,4	6.2±1.3/6.5±1.4	6.2±3.7/8.7±6.6	0.003/0.001
Direct bilirubin (mg/dL)	6±1.7/6.9±1,5	3.6±0.7/4.04±1.1	4.9±4.1/5.8±4.7	0.04/0.02
GGT (IU/L)	204±102/228±145	98±64/67±31	123±78/135±107	0.001/0.001
ALP (IU/L)	202±102/264±134	121±72/142±89	198±93/229±161	0.04/0.03
INR	1.32±0.38/1.45±0.36	1.09±0.18/1.09±0.27	1.49±1.01/1.62±1.03	0.23/0.1

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transpeptidase, ALP: Alkaline phosphatase, INR: International normalized ratio, SD: Standard deviation.

relapsing hepatitis and complicated hepatitis. Although, INR and transaminase levels were found to be higher in children with complicated hepatitis, no statistically significant difference was detected (Table V).

Discussion

The clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. Clinical manifestations of HAV infection are dependent on the age of the patient. In children younger than 6 years of age, about 70% of infections are asymptomatic; in contrast, infection is usually symptomatic, with jaundice and remarkably high levels of serum aminotransferases in more than 70% of adult patients[9]. Similar to the previous studies, in our study, older age was statistically related with atypical manifestations. Additionally, initial and peak levels of AST, ALT, INR, total and direct bilirubin could give statistically significant idea about atypical clinical course progress.

Moreover, to the best of our knowledge, this is the first report from Turkey which evaluated the difference of clinical symptoms between children with typical and atypical HAV infection. Fatigue, nausea/vomiting, jaundice and dark urine were statistically more common in patients with atypical manifestations.

The course of HAV infection could be atypical in forms of cholestatic, recurrent, or fulminant hepatitis, with a percentage of 7%[10]. Atypical clinical manifestations were observed in 1.4% of children with Hepatitis A in the middle region of Turkey[11]. In our study, this percentage was higher (12.8%). In the same study, of the 427 patients, 4 (0.9%) patients were detected to have cholestatic hepatitis. Other atypical manifestations were recurrent hepatitis in 1 (0.2%) patient and fulminant hepatitis in 1 (0.2%) patient[11]. In our study, cholestatic hepatitis, recurrent hepatitis and fulminant hepatitis were found in 21 (5.1%), 14 (3.4%) and 3 (0.7%) of all patients, respectively. These higher percentages can be explained by referred cases with severe or atypical clinical manifestations from the countryside hospitals to our hospital, which is the only reference hospital of the region. Jeong et al[3]. have reported that acute kidney injury was found in 1.5–4.7% of HAV infected pediatric patients in Korea. In our study, no patient was diagnosed by acute kidney injury.

Not surprisingly, in the comparison of children with atypical manifestations jaundice, dark urine, itching and higher initial and peak levels of GGT, ALP, total and direct bilirubin were found to be more frequently in children with prolonged cholestasis. Furthermore, interestingly, children with prolonged cholestasis were statistically older than other two groups. No studies investigating the comparison of demographic, clinical and laboratory findings in children with atypical clinical manifestations of hepatitis A are available in the literature, so far.

In Turkey, hepatitis A vaccination was implemented since November 2012. Our study provides us information about clinical manifestations of HAV infection in children before the implementation of routine hepatitis A vaccination. Therefore, we believe that this study would support serious data for the future studies, which would aim to compare the progress of HAV infections in children before and after the implementation of hepatitis A vaccination in Turkey.

This study includes several limitations. Firstly, it includes only symptomatic patients admitted to pediatric outpatient clinics. For this reason, ratio of atypical clinical manifestations was found higher than other studies. Secondly, due to the small number of patients in groups, comparing the clinical and laboratory findings between prolonged cholestasis, relapsing hepatitis and complicated hepatitis groups was not possible.

As a result, we conclude that older age is the major risk factor for atypical presentation of HAV infections. Higher initial and peak levels of AST, ALT, INR, total and direct bilirubin could predict the atypical manifestation. Also jaundice, dark urine, itching symptoms might help the clinicians to anticipate the atypical clinical course in HAV infected pediatric patients.

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