ORIGINAL ARTICLE

Atypical Clinical Manifestation of Acute Viral Hepatitis A among Children

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Abstract

Background: Hepatitis A virus infection is a tremendous public health problem with a particular incidence in developing countries like Pakistan. The country faces a significant burden of viral hepatitis, with varying rates among provinces due to socio-economic and environmental factors.

Objectives: The primary purpose of this study was to determine the occurrence of atypical manifestations of acute viral hepatitis A infection among children admitted to the National Institute of Child Health in Karachi. Its secondary objective was to determine whether atypical presentations were linked to biochemical or serological modifications.

Methodology: The present prospective case series study was conducted at the National Institute of Child Health in Karachi, Pakistan, from July 2023 to December 2023 enrolled 60 participants, aged between 1 and 15 years, who suffered from acute viral hepatitis A and were positive for the hepatitis A IgM antibody test. All the parents or guardians of the children signed the informed consent form.

Results: The study was conducted on a total of 60 participants, which included 38 males and 22 females. The mean age was 7.89 years (SD = 3.74). Out of these 25 (41.6%) had atypical manifestations including intrahepatic manifestations such as prolonged cholestasis (5.0%), relapse (1.6%), and extrahepatic manifestations such as ascites (10.%), pleural effusion (1.7%), thrombocytopenia (3.3%), skin rash (3.3%), severe anemia (6.7%), aseptic meningitis (3.3%), pericardial effusion (3.3%), and myocarditis 2 (3.3%). Further, revealed that there were significant differences between typical and atypical manifestations of acute viral hepatitis in terms of laboratory parameters including SGPT (p=0.001), total serum bilirubin (p=0.001), direct serum bilirubin (p=0.001), prothrombin time (p=0.001), sodium (p=0.022), and potassium (p=0.022).

Conclusion: This study found that an essential portion of participants had atypical manifestations of AVH-A. Additionally, there were significant differences observed in various laboratory parameters between the typical and atypical manifestation groups, Hence, clinicians should be familiar with and address these atypical manifestations to optimize the outcome and avert potential complications.

Keywords: *Atypical manifestation, acute viral hepatitis A, children.*

INTRODUCTION

Hepatitis A is a widely prevalent form of acute viral hepatitis across the globe. It is commonly transmitted through the fecal-oral route, particularly in developing nations with suboptimal sanitation and hygiene standards [1]. Likewise, the situation is dire in Pakistan; for instance, there are not enough measures for proper hygiene and sanitation, which is the leading cause of around 90% of children in the country becoming victims of Hepatitis A Virus (HAV) before the age of 10 years [2]. In addition, it is reported that in Pakistan, a significant proportion of acute viral hepatitis cases, ranging from 50% to 60%, are attributed to hepatitis A seroconversion in children[3]. Despite the availability of effective and safe vaccines for hepatitis A since 1996, the infection remains a significant cause of acute viral hepatitis worldwide [4].

Hepatitis A is a 27-nm, single-stranded RNA virus classified in the Picornaviridae species [5]. Four separate HAV genotypes have been discovered and identified in humans; however, they are all associated with the same serotype [6]. Children with hepatitis A typically experience fever, exhaustion, appetite loss, nausea, vomiting, diarrhea, and abdominal discomfort, and usually, overall symptoms disappear independently and do not require medical attention [7]. However, these symptoms significantly impact their growth and development [8]. The Hepatitis A Virus (HAV) exhibits a low replication rate and does not induce any apparent cytotoxic effects on the host cells [9]. This pattern consists of a long incubation period of HAV in humans [10]. The incubation period is 15 to 50 days [11], and the average incubation period is reported as 28 days of HAV [12]. There are two phases of HAV, including the pre-icteric and icteric phases. The pre-icteric is characterized by a range of nonspecific symptoms such as loss of appetite, malaise, vomiting, fatigue, fever, abdominal pain, and nausea, and duration ranges from 1 to 14 days. Then, the icteric phase begins, which is marked by jaundice, hepatomegaly, dark urine, and right hypochondrial tenderness[6]; following the icteric phase, most patients will enter the recovery phase; however, in rare cases, patients may experience fulminant hepatic failure[13] However, a particular group of patients might show atypical manifestations; for instance, a study conducted in Bangladesh found that 15% of children

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displayed atypical features of the virus[14]. Similarly, a study conducted in Lahore, Pakistan, in 2014 showed that 35.3% of children exhibited atypical manifestations of acute hepatitis A virus [13]. Another study conducted in Karachi, Pakistan, found that 75% of children under the age of 15 were diagnosed with acute HAV infection [5]. Based on the findings of the literature review, this study was conducted to measure the frequency of atypical manifestations and to investigate the potential correlation between typical and atypical manifestations and biochemical or serological modifications among children diagnosed with acute viral hepatitis A at the National Institute of Child Health Karachi, Sindh, Pakistan.

METHODOLOGY

This prospective case series study was conducted on admitted patients at the National Institute of Child Health in Karachi. The duration of the study was from July 2023 to December 2023. The Institutional Ethical Review Board of NICH Karachi approved the study protocol *via* letter no. IERB-18/2023 dated 16-62023. The study consisted of 60 participants. It is important to note that there is no rigid rule for determining the ideal sample size for a case series study [15]. However, studies showed that the general number of cases reported in a case series ranges from 20 to 50 although this range may extend from just a few cases to over 100 or even thousands [16]. In our study, the observational period was a key consideration in determining the sample size, leading us to Include 60 participants over six months. Before the commencement of the study, informed consent was obtained from parents or guardians. The study comprised children aged between one and fifteen years who were admitted to the National Institute of Child Health in Karachi and were diagnosed with acute viral hepatitis IgM antibody and negative for serological markers of Hepatitis E and B. Further, Children who showed signs of chronic liver disease were omitted. Physical assessment proforma adopted from previous studies [14]; the following tests were included in the proforma: Complete Blood Count (CBC), Liver Function Tests (LFTs), Renal Function Tests (RFTs), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), serum electrolytes, serum albumin, ultrasound of the abdomen, and X-ray of the chest. Daily evaluations were conducted for all patients, and discharged patients were monitored in the outpatient department at two-week intervals until they were fully recovered. Atypical manifestations were observed, and their frequencies were documented during this duration. Further laboratory parameters were measured to assess the variance in typical and atypical manifestations of acute hepatitis A virus patients.

A patient diagnosed with acute Hepatitis A virus based on CDC 2008 criteria: IgM anti-HAV and jaundice or alanine aminotransferase (ALT) values >200 UI/l [17]. Intrahepatic atypical manifestations of HAV are unusual liver symptoms or complications. Extrahepatic atypical manifestations of hepatitis A refer to symptoms or complications that occur outside of the liver and are not commonly associated with hepatitis A infection. These may include neurological, renal, or hematological abnormalities [18]. To confirm these atypical manifestations, we conduct both clinical and investigative assessments. For clinical assessment, we look for the presence of anemia, thrombocytopenia, ascites, and pleural effusion. For investigations, we perform a complete blood count (CBC) to check for anemia or thrombocytopenia, measure serum albumin levels, conduct an ultrasound of the abdomen to check for ascites, perform an ultrasound of the chest to check for pleural effusion, conduct an echocardiogram to check for pericardial effusion or myocarditis, and do a CT scan of the brain to check for aseptic meningitis.

The statistical analysis was conducted using version 29.0 of the SPSS software. Means and standard deviations (SD) were used to present continuous data, while numbers and percentages were used to present discrete variables. A non-parametric Mann-Whitney U test was conducted to determine the significant differences in laboratory parameters between acute viral hepatitis A cases with typical manifestations (n=35) and those with atypical manifestations (n=25). The Chi-square test was used to compare categorical variables between typical and atypical manifestations of acute viral hepatitis A cases. If the p-value was less than 0.05, it was considered statistically significant.

RESULTS

The study included 60 participants, comprising 38(63.3%) males and 22(36.7%) females. In Table **1**, the mean age was 7.89 years (SD = 3.74). Out of these, 35(58.4%) showed typical manifestations, while 25 (41.6%) had atypical manifestations. The participants with atypical manifestations had a significantly higher percentage of individuals aged 3-5 years (44%) than the typical group (20%). On the other hand, the typical group had a higher percentage of children between the ages of 11-15 years (34.3%) compared to the atypical group (20%). There were no significant differences in terms of gender between the two groups. However, the two

Table 1: Demographic comparison of typical *vs.* atypical Acute HAV manifestations.

Characteristic	Typical n(%)	Atypical n(%)	p-value
Age group			
1-2 years	03 (8.6)	0 (0.0)	0.012
3-5 years	07 (20.0)	11 (44.0)	
6-10 years	13 (37.1)	09 (36.0)	
11-15 years	12 (34.3)	05 (20.0)	
Gender			
Male	22(62.9)	16 (64.0)	0.928
Female	13 (37.1)	09 (36.0)	
Geographic Location			
Rural	13 (37.1)	03 (12.0)	0.030
Urban	22 (62.9)	22 (88.0)	

Table 2: Atypical manifestations in hepatitis A patients.

Atypical manifestations	n(%)
Intrahepatic manifestations	
• Prolonged Cholestasis	03 (5.0)
• Relapse	01 (1.7)
Extrahepatic Manifestation	
• Ascites	06 (10.0)
• Pleural Effusion	01 (1.7)
• Thrombocytopenia	02 (3.3)
• Skin Rash	02 (3.3)
• Severe Anemia	04 (6.7)
• Aseptic Meningitis	02 (3.3)
• Pericardial Effusion	02 (3.3)
• Myocarditis	02 (3.3)

groups had a noticeable variation in geographic location. The Atypical manifestation group of children was more commonly found to be residing in urban areas (88%) in comparison to the group with typical manifestations, whose percentage of urban residents is 62.9%. In contrast, the percentage of children living in rural areas was higher in the typical group (37.1%) than in the atypical group (12.0%).

According to Table **2**, atypical manifestations of acute viral hepatitis A were observed in varying frequencies. Intrahepatic manifestations were present in 6% of cases and included prolonged cholestasis (5%) and relapse (1.7%). Meanwhile, extrahepatic manifestations were observed in 16% of cases, such as ascites (10%), severe anemia (6.7%), thrombocytopenia (3.3%), skin rash (3.3%), aseptic meningitis (3.3%), pericardial effusion (3.3%), and myocarditis (3.3%). These findings suggest that acute viral hepatitis A infection can present with a variety of clinical manifestations beyond liver involvement, emphasizing the need for vigilant monitoring and management of affected individuals.

Table **3** A non-parametric Mann-Whitney U test revealed significant differences in the laboratory parameters of typical (n=35) and atypical (n=25) manifestations of acute viral hepatitis A cases. such as SGPT (U= 63 , z=-5.62, r=0.72, p=0.001), total serum bilirubin (U= 171, Z=-4.02, r=0.001, p=0.001), direct serum bilirubin (U=216.5, Z-3.44, r=0.44, p=0.001), prothrombin time (U=99.5, Z=-5.11, r=0.65, p=0.001), sodium (U=287.5, Z=-2.29, r=0.29, p=0.022), and potassium (U= 287.5, Z=-2.28, r=0.29, p=0.022). However, there were no significant differences in albumin (U=422.5, Z=-0.22, r=0.02, p=0.820) and hemoglobin (U= 433.5, Z=-0.06, r=0.00, p=0.949) levels. These findings suggest that there are significant differences in certain parameters/ variables between typical and atypical cases, which could be useful in diagnosing and treating patients with acute viral hepatitis A virus and liver diseases.

Table 3: Comparison of laboratory findings in children with typical and atypical manifestation of acute viral hepatitis A.

Parameters/ variables	Typical (n= 35) Median	Atypical (n= 25) Median	Mann-Whitney U	Z score	(r)* score	*p-value
SGPT (IU/L)	650.0	1400.0	63.0	-5.62	0.72	0.001
Total serum bilirubin (mg/dl)	3.0	5.0	171.0	-4.02	0.51	0.001
Direct serum bilirubin (mg/dl)	2.0	2.50	216.5	-3.44	0.44	0.001
Prothrombin time (seconds)	12.0	20.0	99.5	-5.11	0.65	0.001
Albumin(gram/dl)	2.8	2.5	422.5	-0.22	0.02	0.820
Hemoglobin (g/dL)	8.0	8.0	433.5	-0.06	0.00	0.949
Sodium (mmol/L)	137.0	140.0	287.5	-2.29	0.29	0.022
Potassium (mEq/L)	3.6	3.2	287.5	-2.28	0.29	0.022

*r = score indicated the effect size of the difference between the two groups. *Significant at p<0.05

DISCUSSION

This is the first study at the National Institute of Child Health in Karachi, Pakistan, to measure acute viral hepatitis A infection in children with typical and atypical manifestations. According to our research findings, a significant proportion (41.6%) of patients revealed atypical manifestations beyond liver involvement. Furthermore, up to 16% of cases demonstrated extrahepatic symptoms like ascites, severe anemia, and skin rash. Previous studies have shown that 14% to 49% of pediatric patients diagnosed with acute hepatitis A virus reported atypical manifestations [14, 19-21]. Acute viral hepatitis A atypical manifestations may be caused by an inappropriate immune response [13]. However, the exact mechanism remains unknown despite several studies on this matter [14, 19-21]. Further, we did not find gender and age group differences in our study similar to study-reported findings [14].

Moreover, prolonged cholestasis was a common intrahepatic manifestation of the atypical presentation of our study. There was notable variation in the duration of cholestasis among cases, with some patients experiencing symptoms for several weeks while others reported persistence for up to a month. In supporting our findings, other studies also endorsed similar reports [14, 19-21]. Additionally, we frequently observed ascites as a common finding in children with atypical extrahepatic manifestations. Similarly, studies reported a notable prevalence of ascites in children with acute hepatitis A virus [21, 22]. Its presence can indicate the severity of the underlying disease and can guide the choice of treatment. Therefore, Clinicians need to be aware of this association and consider ascites as a potential complication in children with atypical manifestations. Further research is required to understand the pathophysiology of ascites in children and improve its diagnosis and treatment.

Regarding laboratory parameters, patients with atypical manifestations showed higher levels of SGPT, serum bilirubin (total and direct), and prothrombin time. Another research similarly discovered increased blood bilirubin and SGPT levels in patients with atypical manifestations [14]. SGPT and bilirubin levels in the blood are frequently

used to monitor the condition of the liver [23]. Our findings show that these markers can be used to detect and treat people with atypical manifestations of acute viral hepatitis A or liver-related problems.

This study found that blood albumin levels substantially fluctuated in both conditions of acute viral hepatitis A. Liver hepatocytes synthesize albumin and rapidly excrete it into the bloodstream at the rate of about 10 gm to 15 gm per day [24]. Although albumin is necessary for sustaining oncotic pressure in the body, a low level of serum albumin indicates a poor prognosis in various medical conditions [25]. Therefore, monitoring serum albumin levels can help predict the outcome of patients with acute viral hepatitis A and individual nutritional status.

CONCLUSION

The study revealed that acute viral hepatitis A presents significant atypical manifestations, including intrahepatic manifestations that consist of prolonged cholestasis and relapse. In addition, extrahepatic manifestations include ascites, pleural effusion, thrombocytopenia, skin rash, severe anemia, aseptic meningitis, pericardial effusion, and myocarditis. Furthermore, we observed significant variations in biochemical parameters, including SGPT, prothrombin time, and serum bilirubin (both total and direct), as well as sodium and potassium levels, between patients with atypical manifestations and those with typical manifestations of acute viral hepatitis A.

The findings of this study have significant implications for healthcare practitioners who treat individuals with acute viral hepatitis A. Furthermore, the study emphasizes the significance of closely monitoring individuals with atypical manifestations since they may be at a higher risk of consequences and require more intensive therapy. The study also stresses the need for further research into the underlying mechanisms responsible for atypical manifestations in acute viral hepatitis A infection. This can help us understand the illness's etiology and devise more effectively.

ETHICS APPROVAL

Ethical approval was obtained from the Institutional Ethical Review Board (IERB) of the National Institute of Child Health (NICH), Karachi (REF letter No. IERB-18/2023). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the parents/ guardians of participants.

AVAILABILITY OF DATA

The data used to support the findings of this study is available from the corresponding author upon request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTION

Shafqat Ali and Arit Parkash conceptualized and prepared the original draft and methodology. Sadam Hussain collected data, reviewed articles, and edited the document. Bilquis Naeem performed formal data analysis and wrote the first draft. Arit Parkash supervised and gave final approval. All authors have read and agreed to the published version of the manuscript.

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