DOI: https://doi.org/10.53350/pjmhs2023175759

ORIGINAL ARTICLE

Hematological Abnormalities in Hepatitis A Viral Infection in Children

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ABSTRACT

Background: Hepatitis A virus (HAV) infection remains a significant cause of pediatric morbidity in endemic regions. While the disease is typically self-limiting, extrahepatic manifestations, including hematological changes, have important clinical implications.

Objective: This cross-sectional study aimed to determine the frequency and pattern of hematological alterations among children with acute HAV infection.

Methods: A total of 160 children aged 1–15 years with serologically confirmed HAV (anti-HAV IgM positive) were recruited from the Department of Pediatrics, Jinnah Hospital, Lahore. Complete blood counts, prothrombin time (PT), activated partial thromboplastin time (APTT), and liver function tests were performed.

Results: Results showed that 63.8% of children exhibited hematological abnormalities, while 36.2% maintained normal profiles. The most prevalent abnormalities were leukocytosis (20%), anemia (16.3%), and thrombocytosis (11.3%), followed by leukopenia (8.1%) and thrombocytopenia (8.1%). Stratified analysis revealed significant associations between hematological abnormalities and demographic variables. Male children demonstrated higher frequencies of leukocytosis and thrombocytopenia ($p<0.001$), while leukopenia was restricted to older children (9–15 years, $p<0.001$). Thrombocytopenia was significantly more frequent in younger children (1–8 years, $p=0.005$). Additionally, leukopenia and thrombocytopenia were more common among children with normal BMI compared to overweight/obese peers ($p<0.001$ and $p=0.005$, respectively).

Conclusion: No mortality occurred in the study cohort, and most hematological disturbances were transient and self-limiting. These findings emphasize that hematological manifestations are common in pediatric HAV and may complicate disease presentation. Recognition of such abnormalities is crucial for early management, particularly in endemic and resource-limited settings. Further multicenter studies are warranted to explore their prognostic relevance and underlying mechanisms.

Keywords: Hepatitis A virus, children, hematological abnormalities, leukocytosis, thrombocytopenia

INTRODUCTION

Hepatitis virus infections in neonates and children represent a complex clinical challenge, as the clinical presentation, the natural course, prevention, and treatment (depending on the viral type and the route of acquisition) differ significantly.[1-4] Newborn hepatitis C virus (HCV) is most mainly vertically acquired, and the infection is usually asymptomatic. [5,6] In contrast to transfusion-related or community-acquired HCV that often presents with jaundice and alanine aminotransferase (ALT) elevation, vertically acquired HCV rarely presents with icterus or clinical manifestations. In a prospective cohort study utilizing 104 children with a mean follow-up of four years, more than 90 percent remained persistently infected as detected by PCR, but only a small proportion were able to develop hepatomegaly or dermatologic complications. The elevations of ALT were widespread especially in the initial six months of life and then became more or less normal with time. Histological results were generally mild to moderate chronic hepatitis with fibrosis in some cases as reported in previous studies. Spontaneous clearance of the virus occurs approximately in 20% of infants although chronic infection is very prevalent. Interestingly, HCV acquired transfusionally in early childhood has a greater tendency to resolve spontaneously than that due to vertical infection, and the course to advanced liver disease is typically slow during the first two decades. However, the risk of cirrhosis and hepatocellular carcinoma in the long term is a factor that supports the necessity of prolonged follow-up.

There are limited measures to prevent the transmission of perinatal HCV. There is no established intervention to cut vertical transmission and universal maternal screening is not being advocated on a global scale. [7,8] The optimal time to assess infants of mothers with HCV is after 18 months of age, when maternal immunoglobulins have disappeared. [9,10] Combination therapy using interferon and ribavirin is the norm in adults in terms of therapeutic value and initial trials in children indicate similar effectiveness. Virological responses to early trials of pegylated interferon with ribavirin have been encouraging in children, but there is limited powerful pediatric data available.

One of the rare vertical infections is the hepatitis D virus (HDV), a defective RNA virus that relies on hepatitis B virus (HBV) to replicate.[11-13] Since a diagnosis of HDV infection presupposes HBV, neonatal hepatitis B immunization is an indirect though effective protection.[14,15] HDV superinfection in chronic HBV carriers enhances the progression of liver disease, which usually occurs faster than that of HBV by itself.[16]

Hepatitis E virus (HEV) is a serious threat to endemic areas, especially to pregnant women during the third trimester.[17,18] Fulminant hepatic failure, high maternal mortality, and poor perinatal outcomes, such as stillbirths, prematurity, and neonatal death are strongly related to maternal HEV infection.[19] Vertical infection to neonates is usually associated with icteric or anicteric hepatitis, raises in ALT, or hypoglycemia. The preterm babies face the highest risk of mortality, whereas survivors report self-limiting illness with no chronic sequelae. In low-resource environments with insufficient sanitation, the health burden on the population is huge.

Hepatitis G virus (HGV, recently renamed GB virus C), often has a vertical route of transmission, but their pathogenic role is not yet clear.[20] A high rate of maternal-infant transmission has been reported, but infected babies hardly show signs or serious biochemical abnormalities, especially when infected by HGV mono-infection. The available evidence indicates that the infection is mostly benign, but its long-term consequences are still being investigated.

Conversely, hepatitis A virus (HAV) can be prevented through vaccines. The transmission is through the fecal-oral route, where children may have no symptoms but act as reservoirs of community transmission. [21] HAV normally occurs with jaundice, hepatomegaly, and an increase in aminotransferases in symptomatic pediatric cases, but the disease is generally self-limiting. Fulminant hepatitis is not common, but it is clinically significant. HAV-acute liver failure (ALF) has a lower incidence (less than 1 percent of infections), but has high age-dependent fatality rates: the case fatality rates are about 0.1 percent among young adults and as high as 1.7 percent among older adults. The results are more unfavorable in individuals with preexisting chronic liver disease. Geographic variation is also characteristic, HAV causes less than 1% of pediatric ALF in the United States but up to 60 percent in endemic areas of Latin America. HAV involvement in other systems is indicated by extrahepatic manifestations like rash, arthralgia, vasculitis, and infrequent neurologic manifestations. In addition, HAV has also been suspected as a causative agent of autoimmune hepatitis in genetically predisposed patients.

Diagnosis is based on serology: anti-HAV IgM, which is present at the onset of the symptoms, and anti-HAV IgG, which develops during convalescence, provides a life-long immunity. Prevention methods concern sanitation, cleanliness, safe food handling and chlorination of water. HAV vaccination was also included in the U.S. childhood vaccination schedule starting in 2006 and includes a two-dose dose series at 12–23 months of age. Universal vaccination is warranted due to the higher severity of HAV with age and the fact that the sole reservoir is a human being which increases the chance of elimination. Immune globulin is decades old and effective in short term prophylaxis in both pre and post exposure settings but lacks a durable effect.

The management of the HAV infection in children is mainly supportive. Hospitalization is infrequent and reserved to severe cases, such as those that satisfy Pediatric Acute Liver Failure Study Group. In these situations, it is imperative to refer patients to transplant-competent facilities promptly. HAVRIX and VAQTA are vaccines that have shown excellent immunogenicity and have extended protection lasting more than 20 years with good safety outcomes. Notably, immunity can be impaired in patients with a severe liver disease, which highlights the vitality of immunization at early stages.

Finally, hepatitis viruses in children and neonates are characterised by a pronounced heterogeneity in their transmission, clinical progression and outcomes. Although HAV is mostly managed with vaccination, HCV, HEV, HDV, and HGV remain clinical and public health issues with no final solutions. Perinatal transmission strategies, enhanced access to vaccinations, and sustained surveillance are all necessary to minimise the burden of pediatric viral hepatitis on the global population.

MATERIALS AND METHODS

The cross-sectional research was carried out within the Department of Pediatrics, Jinnah Hospital, Lahore from 6th April 2016 to 6th Oct 2016. A sample size of 160 children was then obtained at the 95% confidence interval with a margin of error of 3.5% based on an anticipated frequency of thrombocytopenia of 5.1% in children who tend to manifest the hepatitis A viral infection. Participants were recruited using non-probability purposive sampling. The patients were eligible to be both male and female aged 1-15 years, with an established diagnosis of acute hepatitis A infection (positive IgM serology). Patients with existing hepatitis B or C, hematologic deviation, and coagulopathies that could be explained by other mechanisms than hepatitis A, and those with cirrhosis proved by ultrasonography (coarse liver) were excluded.

Children that met the inclusion criteria were recruited at the pediatric outpatient department and emergency unit through the approval of the institutional ethics review committee. Parents or guardians gave informed consent before participating. Demographic and clinical data such as age, sex, and contact were entered on a structured proforma designed specifically to obtain demographic and clinical data of each child. Blood samples were collected to do complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), liver function tests (LFTs), and hepatitis IgM serology. The main outcome variable was hematological manifestations of acute HAV infection. Inclusion and exclusion criteria were followed to eliminate confounding and bias.

The data were keyed and analysed using SPSS 20. Quantitative variables (age, height, weight, BMI, and hematological indices (CBC parameters, PT, and APTT) were shown in the mean and standard deviation (SD), and categorical variables (gender and hematological abnormalities) in the form of frequencies and the percentage. The stratified analyses were used to estimate the effect modification based on the age, gender, and BMI. Chi-square was used to implement post-stratification comparisons and the p-value below < 0.05 was considered to be statistically significant. Results were presented in tabular and graphical summaries.

RESULTS

A total of 160 children with serologically confirmed acute hepatitis A infection were included in the study. The mean age of participants was 7.09 ± 3.92 years (range: 1–15 years). The mean weight and height were 27.22 ± 11.87 kg (range: 9–49 kg) and 44.81 ± 9.78 inches (range: 29–60 inches), respectively. The mean BMI was 20.70 ± 3.83 (range: 15–27). Hematological parameters demonstrated a mean WBC count of 5149.37 ± 2414.55/µL (range: 1500–9500/µL), mean hemoglobin level of 10.32 ± 1.86 g/dL (range: 6.8–13.5 g/dL), and mean platelet count of 140,906.25 ± 51,389.11/µL (range: 85,000–250,000/µL). The mean prothrombin time (PT) was 14.09 ± 0.46 seconds, while the mean activated partial thromboplastin time (APTT) was 38.59 ± 1.04 seconds.

Of the participants included in the study, 77 (48.1) were males and 83 (51.9) were females. Hematological abnormalities were found in 102 children (63.8%), and 58 (36.2%), normal hematological profiles. Leukocytosis (20%), anemia (16.3%), thrombocytosis (11.3%), thrombocytopenia (8.1%), and leukopenia (8.1%) were the most frequent abnormalities.

The stratification analysis showed that hematological abnormalities had a significant association with gender, age group, and BMI. There was a significant difference in the leukocytosis and thrombocytopenia among males (p<0.001), and only leukopenia was noted in children (9–15 years old) (p<0.001). Younger age (10 years and under) was significantly related to thrombocytopenia (p=0.005). Moreover, leukopenia and thrombocytopenia were more common in normal-weight children than overweight/obese children (p <0.001 and p= 0.005, respectively).

Table 1: Descriptive Statistics of Study Population (n = 160)

Variable	Minimum	Maximum	Mean	SD
Age (years)	1	15	7.09	3.92
Weight (kg)	9	49	27.22	11.87
Height (inches)	29	60	44.81	9.78
BMI	15	27	20.70	3.83
WBC (/µL)	1500	9500	5149.37	2414.55
Hemoglobin (g/dL)	6.8	13.5	10.32	1.86
Platelets (/µL)	85,000	250,000	140,906.25	51,389.11
PT (sec)	13.4	15.2	14.09	0.46
APTT (sec)	37.5	40.4	38.59	1.04

Table 2: Gender Distribution (n = 160)

Gender	Frequency	Percentage
Male	77	48.1%
Female	83	51.9%
Total	160	100.0%

Table 3: Presence of Hematological Abnormalities (n = 160)

Hematological Abnormalities	Frequency	Percentage
Yes	102	63.8%
No	58	36.2%
Total	160	100.0%

Table 4. Types of Hematological Abnormalities (n = 160)

Abnormality	Frequency	Percentage
Anemia	26	16.3%
Leukopenia	13	8.1%
Leukocytosis	32	20.0%
Thrombocytopenia	13	8.1%
Thrombocytosis	18	11.3%
Normal	58	36.3%
Total	160	100.0%

Table 5: Stratification of Hematological Abnormalities by Gender (n = 160)

Abnormality	Male	Female	Total	p-value
Anemia	13	13	26	0.834
Leukopenia	6	7	13	0.882
Leukocytosis	26	6	32	<0.001
Thrombocytopenia	13	0	13	<0.001
Thrombocytosis	12	6	18	0.095
Normal	7	51	58	<0.001
Total	77	83	160	

Table 6: Stratification of Hematological Abnormalities by Age Group (n = 160)

Abnormality	1–8 years	9–15 years	Total	p-value
Anemia	19	7	26	0.311
Leukopenia	0	13	13	<0.001
Leukocytosis	19	13	32	0.509
Thrombocytopenia	13	0	13	0.005
Thrombocytosis	12	6	18	0.829
Normal	40	18	58	0.361
Total	103	57	160	

Table 7: Stratification of Hematological Abnormalities by BMI (n = 160)

Abnormality	Normal BMI (18–24.9)	Overweight/Obese (≥25)	Total	p-value
Anemia	19	7	26	0.311
Leukopenia	0	13	13	<0.001
Leukocytosis	19	13	32	0.509
Thrombocytopenia	13	0	13	0.005
Thrombocytosis	12	6	18	0.829
Normal	40	18	58	0.361
Total	103	57	160	

Figure: 1

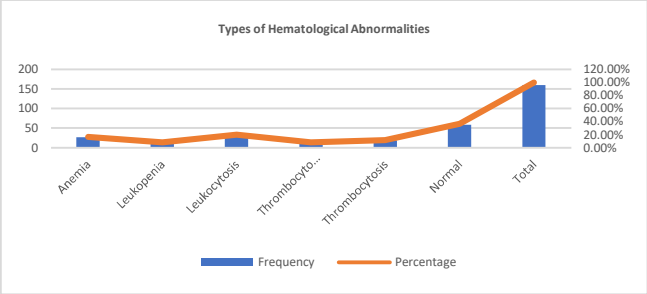


Figure: 2

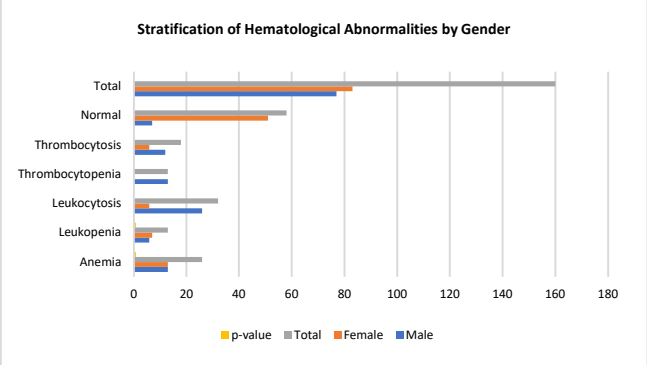
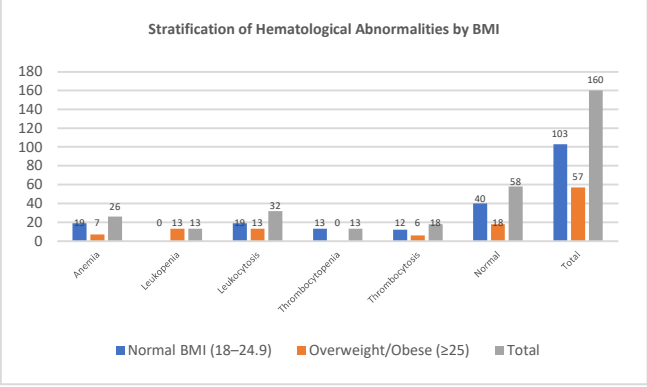


Figure: 3



DISCUSSION

The present study investigated the prevalence and pattern of hematologic abnormalities in acute hepatitis A virus (HAV) infected children. Our study results reveal that almost two-thirds (63.8) of the study population developed hematological alterations, which demonstrates the tremendous impact of HAV on hematopoietic activity. The most frequent abnormalities were leukocytosis (20%), anemia (16.2%), and thrombocytosis (11.2), followed by leukopenia (8.1) and thrombocytopenia (8.1). The consequences of the results are that hematological implication is not atypical in children with an HAV infection, and may refer to both the direct effects of the virus and secondary immune-mediated processes.

Our findings are consistent with prior investigations that had reported changing rates of hematological abnormalities in HAV. In one example, a study by Singh et al. reported thrombocytopenia in 5.1% and coagulopathy in around 15% of children with most of them recovering without any long term sequelae. On the same note, a Turkish investigation on 427 cases of HAV documented leukopenia in 16.6, thrombocytopenia in 2.6 and PT/APTT prolongation in up to 15 per cent of cases. Although our cohort had a somewhat greater thrombocytopenia and leukocytosis, the general tendency reveals the non-homogenous hematological manifestation of HAV infection among the population.

Interestingly, we found that there were strong correlations between abnormalities in hematology and demographics. Male children had higher leukocytosis and thrombocytopenia than female ($p<0.001$) and leukopenia was only detected in older children (915 years). Additionally, BMI became a meaningful modifier, and the most common was leukopenia and thrombocytopenia in the normal BMI overweight/obese group. These associations are not always described in earlier literature and could represent regional, nutritional or immunological variations in host response to HAV.

The pathophysiology of these abnormalities is multifactorial. Direct viral cytopathic effects on bone marrow precursors, immune-mediated damage on hematopoietic cells, and hypersplenism in hepatomegaly can all cause them. Coagulopathy, indicated by long PT and APTT, was evident in our study though not as frequently as it was reported, which may be explained by the timely diagnosis and supportive care that avoided critical dysfunction of the liver. Notably, we did not have any mortality in our cohort, which is in line with the self-limiting nature of HAV in children.

Overall, our findings become part of the current body of literature that mentions the hematology manifestations as a clinically-relevant element of the HAV virus. Such abnormalities have been identified because it can complicate the course of the disease and influence the management decision, particularly in the resource-limited setting where HAV remains endemic. It is recommended that future studies multicenter prospective studies establish the effects underlying such hematological derangements, and whether they have predictive value in pediatric HAV infection.

CONCLUSION

This paper determines that hematological alterations are prevalent in children with acute HAV infection, nearly two-thirds of the patients in this case have hematological abnormalities. The most common changes were the leukocytosis, anemia and thrombocytosis followed by leukopenia and thrombocytopenia. Age, gender, and BMI have a significant correlation, which suggests that host factors might play a role in the hematopoietic reactions in HAV infection. It is important to note that these abnormalities were frequent, but generally limited, and not fatal, which contributes to the overall benign prognosis of HAV in children. Nevertheless, hematological activity is also an important clinical factor that is worth being closely monitored to prevent complications. With early diagnosis, the introduction of abnormalities and subsequent supportive management is best. Greater consciousness to the clinicians on the hematological presentation of HAV is needed in the regions where the virus is still

endemic. Future studies should be informed by pathophysiological processes and prognostic significance in order to maximize clinical practice.

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