Original Article

Prognostic Value of Porta-Hepatis Lymphadenopathy in Children with Hepatitis A

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Abstract

Background: The present study aimed to investigate the prognostic value of porta-hepatis lymphadenopathy (PHL) in children with hepatitis A virus. **Methods:** The present prospective cohort study included 123 pediatric patients with a definite diagnosis of hepatitis A who were divided into two groups based on the presence or absence of PHL in their abdominal ultrasound: Group A included the patients with a porta-hepatis lymph node of >6 mm in diameter, whereas the patients with a porta-hepatis lymph node of <6 mm in diameter were classified in Group B. The patients were also classified based on the presence or absence of para-aortic lymphadenopathy: Group C had bisecting para-aortic lymph nodes, whereas Group D did not have such findings in their ultrasound. Afterward, the groups were compared in laboratory investigation results and hospital stay. **Results:** According to our results, Group A ($n = 57$) was significantly higher in aspartate and alanine aminotransferase and alkaline phosphatase levels compared to Group B ($P < 0.05$), whereas these two groups were not significantly different in the hospital stay. Furthermore, except bilirubin, all laboratory test results were significantly higher in Group C ($n = 3$) than in Group D. However, there was no significant correlation between the patients' prognosis with the absence or presence of porta-hepatis or para-aortic lymphadenopathy. **Conclusion:** We concluded that there was no significant relationship between porta-hepatis or para-aortic lymphadenopathy and the prognosis of the children with hepatitis A. However, ultrasound findings can help determine the disease severity in pediatric patients with hepatitis A.

Keywords: Hepatitis A, lymph node, pediatric, porta-hepatis, ultrasound

Introduction

Tens of millions of viral hepatitis cases, including more than one million cases of hepatitis A, are annually diagnosed all over the world, imposing a heavy economic burden on health-care systems globally.[1,2] The incidence of hepatitis A was used to be higher in low-income countries. However, this demographic pattern has changed recently.[3-5]

Acute hepatitis A is diagnosed using serological testing for anti-hepatitis A virus (HAV) immunoglobulin M (IgM). Moreover, an ultrasound is often performed in pediatric patients with acute hepatitis A to confirm the diagnosis and rule out other causes of elevated liver enzymes.[6-8] The common ultrasound findings in this disease include hepatic enlargement, periportal hyperechogenicity, and gallbladder wall thickening (GWT). Furthermore, it is well recognized that porta-hepatis lymphadenopathy (PHL) is another common ultrasound finding in hepatitis A, particularly in pediatric patients.[9-12] However, healthy individuals may also have a lymph node in the porta-hepatis.[12,13] In such benign cases, PHL does not exceed 6 mm in diameter on ultrasound.[14,15]

For decades, the relationship between ultrasound findings and the prognosis of patients with hepatitis A has been contemplated. The basic imaging criteria for HAV include objective ultrasound findings, such as decreased liver echogenicity, a bright periportal echo, and hepatomegaly. However, these findings are all fairly complex. Thus, several recent studies have focused on the measurable findings in ultrasound, such as GWT. Moreover, some studies have

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Received: 30-10-2021 **Revised:** 08-12-2021 **Accepted:** 27-01-2022 **Available Online:** 22-09-2022

Access this article online

Quick Response Code:

Website: www.jmuonline.org

DOI: 10.4103/jmu.jmu_196_21

How to cite this article: Mashhadi A, Khalili M, Moghaddam AA, Zadehmir M. Prognostic value of porta-hepatis lymphadenopathy in children with hepatitis A. J Med Ultrasound 2022;30:272-6.

evaluated the relationship between GWT and biochemical parameters or even clinical deterioration of the patients with acute hepatitis.[7-9]

As an ultrasound finding, the prognostic value of PHL has not been adequately investigated in pediatric patients with HAV. Given the limited studies performed on pediatric patients with HAV, the studies on adult patients are the only available evidence, particularly those performed on patients with chronic hepatitis.[16-20] Therefore, the present study aimed to bridge this gap by investigating the clinical significance of PHL in children with hepatitis A.

Materials and Methods

The present prospective cohort study was conducted at the department of radiology of a general academic hospital from April 2018 to March 2020. The study included 123 patients younger than 18 years old who were admitted to the gastroenterology ward of the same hospital with a diagnosis of acute hepatitis A. These patients had presented with new-onset jaundice, abdominal pain, nausea, vomiting, elevated liver enzymes, and changing liver function tests and were referred by the pediatric gastroenterologist for serological testing. Afterward, those positive for the virus-specific IgM antibodies were considered the confirmed cases of hepatitis A and were included in the study. Furthermore, the patients whose symptoms lasted for more than 1 week and those with obstructive jaundice, cirrhosis, chronic hepatitis disease, and history of cholecystectomy or cholelithiasis were excluded from the study.

Within 2 days of hospital admission, the patients underwent abdominal ultrasound twice by two radiologists blinded to the laboratory testing results of the patients. The ultrasound device had a low frequency (5MHz) convex transducer of GE Voluson E10 (GE Healthcare) using high-resolution B mode. Ultrasound examination required full knowledge of the exact anatomy of the hepatic hilum. The porta-hepatis lymph node was considered an ovoid mass of tissue isolated from the surrounding vessels or organs and was equal to or less echogenic than the hepatic parenchyma in transverse, oblique, and longitudinal views of ultrasound. The lymph node was located between the inferior vena cava and the portal vein.[17-21] At first, the patient was positioned in the supine or left decubitus positions to measure the short axis of the porta-hepatis lymph node [Figure 1]. Afterward, a standard transverse view along the midline was used to evaluate the para-aortic lymph nodes. Any lymph node located in the porta-hepatis region with a mean short-axis diameter of higher than 6 mm, which was measured by two independent radiologists, was considered significant lymphadenopathy. It is worth noting that para-aortic lymphadenopathy is not a common ultrasound finding in patients with hepatitis A. Therefore, any lymphadenopathy could indicate a pathologic condition and was recorded.

The study participants were divided into two groups based on the presence or absence of PHL in their abdominal ultrasound: Group A included the patients with a porta-hepatis lymph node of >6 mm in diameter, whereas the patients with a porta-hepatis lymph node of <6 mm in diameter were classified in Group B. The patients were also classified based on the presence or absence of para-aortic lymphadenopathy in their ultrasound: Group C had bisecting para-aortic lymph nodes, whereas Group D did not have such findings in their ultrasound. Data collection was performed by the senior radiology resident using a predesigned checklist, including demographics, laboratory findings (aspartate aminotransferase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], prothrombin time [PT], international normalized ratio [INR], and total and direct bilirubin), and hospital stay. Afterward, the groups were compared based on their mean values of laboratory investigations and hospital stay.

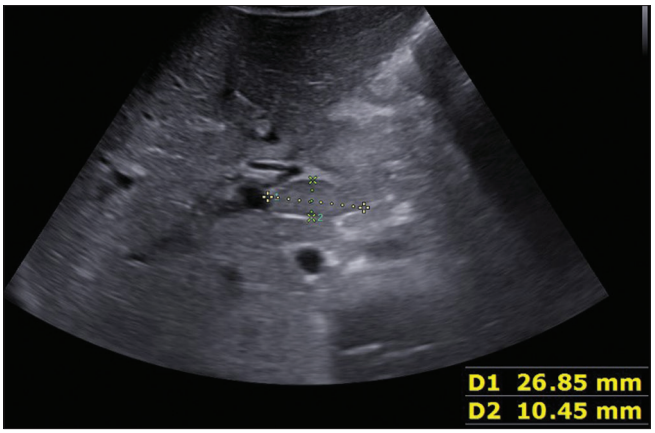

Figure 1: A 5-year-old male with acute hepatitis A. Longitudinal ultrasound view of liver shows porta-hepatis lymphadenopathy

This present study was approved by the local ethics committee (approval number: IR.ZAUMS.REC.1397.235). The patients and their parents were fully explained about the study objectives. Moreover, the patients' parents gave written informed consent before the assessments.

The continuous variables were described using the mean and standard deviation as the central and dispersion indices, respectively. Moreover, the correlations between biochemical variables and ultrasound findings were investigated using the independent *t*-test. Furthermore, the multivariate logistic regression analysis was used to determine the dimensions related to the lymph node size. The significance level was set at 0.05, and data analysis was performed using the SPSS software 26.0 (SPSS Inc., Chicago, IL, USA).

Results

The present study included pediatric patients admitted to a general academic hospital with typical symptoms of acute hepatitis A and a positive serological test for HAV. Of a total of 123 patients who met the eligibility criteria of the present study, 52% were female (n = 64). The participants' mean age was 6.71 years, with an age range of 1–16 years. The abdominal ultrasound findings in the study participants included GWT,

Table 1: Clinical and laboratory findings for patients with porta-hepatis lymph node ≤6 mm and >6 mm

Characteristic	Patients with porta-hepatis lymph node >6 mm (Group A, *n*=57)	Patients with porta-hepatis lymph node ≤6 mm (Group B, *n*=66)	*P*
Age (years)	6.68±3.05	6.73±3.75	0.935
Hospitalization duration (days)	4.75±2.00	4.81±2.20	0.868
AST (IU/L)	1145.06±1150	657.24±632	0.004*
ALT (IU/L)	1252.94±801	904.98±723	0.013**
Total bilirubin (mg/dl)	9.12±9.25	8.36±10	0.674
Direct bilirubin (mg/dl)	5.09±3.89	5.13±5.94	0.965
Albumin (IU/L)	4.02±0.40	4.03±0.46	0.850
ALP (IU/L)	1258.77±673	904.12±577	0.002***
INR	1.07±0.14	1.07±0.17	0.957

AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, *,**,***: Significant

which was observed in 83% of the patients ($n = 103$), and PHL, observed in 71% of the patients ($n = 88$).

The mean diameter of the short axis of porta-hepatis lymph nodes was 5.50 ± 3.93. Moreover, the mean values of AST, ALT, and ALP were significantly higher in Group A compared to Group B [$P < 0.05$, Table 1]. However, the study groups were not significantly different in other laboratory parameters and hospital stay. Furthermore, the multivariate logistic regression analysis showed that AST and ALP levels had a significant relationship with PHL [Table 2]. A significant association was found between PHL and GWT using the Chi-squared test [$P = 0.010$, Table 3].

According to our results, para-aortic lymphadenopathy was observed in 2.4% of the participants ($n = 3$) and included lymph nodes of 4–8 mm in diameter. Moreover, there was a significant correlation between AST, ALT, ALP, albumin, and PT (INR) levels with the para-aortic lymphadenopathy [$P < 0.05$, Table 4]. However, para-aortic lymphadenopathy had no significant effect on hospital stay. Furthermore, multivariate logistic regression showed that the ALP and albumin levels were significantly higher in the patients with para-aortic lymphadenopathy [Table 5].

Table 2: Multivariate analysis of associated factors associated with porta-hepatis lymph node

Characteristic	OR	95% of CI		*P*
		Lower	Upper	
AST	1.001	1.000	1.001	0.049*
ALT	1.000	0.999	1.001	0.795
ALP	1.001	1.000	1.001	0.041**

AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, CI: Confidence interval, OR: Odds ratio, *,**: Significant

Discussion

According to our findings, PHL was a common ultrasound finding in pediatric patients with acute hepatitis A (71%), which was compatible with a previous study reporting a prevalence of 100% for this finding in the patients with hepatitis A.[10]

Moreover, the present study aimed to investigate the prognostic value of PHL in hepatitis A. We found that the patients with PHL had higher AST, ALT, and ALP levels than those without PHL. However, such differences were only significant for ALP and AST. Furthermore, PHL had no significant relationship with other laboratory investigation results and hospital stay. These results indicated that the size of PHL had a close relationship with the severity of hepatic enzyme elevation in the study participants.

Another finding of the present study was that PHL had a significant correlation with AST and GWT, confirming the indirect relationship between GWT and AST. This finding was compatible with several studies reporting a direct correlation between GWT in ultrasound and elevated AST and ALT levels.[9-23] On the other hand, some other studies did not find a clear relationship between serum transaminase levels and GWT. However, they reported a correlation between bilirubin (T/D) levels and GWT.[10,22]

Few studies have reported the prognostic value of PHL in pediatric patients with hepatitis A compared to adult patients with chronic hepatitis B and C. Moreover, some studies have investigated the prognostic value of GWT in these pediatric patients.[9,10-22,23] Other studies have investigated the perihepatic lymphadenopathy in chronic hepatitis, showing a relationship between perihepatic lymph node index and serum AST and ALT levels in patients with chronic hepatitis.[24] Such an index can predict the histopathological inflammation of the liver in patients with hepatitis B and C.[16-20]

According to our results, three patients (2.4%) had para-aortic lymph nodes, all of which were <10 mm in diameter. Lymph nodes are oval-shaped and normal-appearing cortex preserved by hilum. As mentioned before, we also classified the patients based on their para-aortic lymphadenopathy so that those with bisecting para-aortic lymph nodes were considered Group C, whereas those without such findings were considered Group D. Moreover, no patient had any symptoms in the follow-up ultrasound performed 6 months later. Para-aortic lymphadenopathy is not a common finding in patients with hepatitis, especially hepatitis A. However, it is not suggestive

Table 3: The relationship between the gallbladder wall thickening and for patients with porta-hepatis lymph node ≤6 mm and >6 mm

Characteristics	Porta-hepatis lymph node >6 mm (Group A, *n*=57)	Porta-hepatis lymph node ≤6 mm (Group B, *n*=66)	Total	P
GWT (mm)				
<3	4	16	20	0.010*
≥3	53	50	103	

GWT: Gallbladder wall thickening, *: Significant

Table 4: Clinical and laboratory findings for patients with and without para-aortic lymph node

Characteristic	Patients with para-aortic lymph node (Group C, *n*=3)	Patients without para-aortic lymph node (Group D, *n*=120)	*P*
Age (years)	9±2.64	6.65±3.44	0.244
Hospitalization duration (days)	4.00±0.00	4.80±2.12	0.513
AST (IU/L)	2042±1881.75	854±898.98	0.030*
ALT (IU/L)	2108±1248.50	1040±751.42	0.018**
Total bilirubin (mg/dl)	7.23±4.01	8.75±10.11	0.797
Direct bilirubin (mg/dl)	4.53±1.28	5.12±5.13	0.842
Albumin (IU/L)	4.56±0.81	4.01±0.42	0.032***
ALP (IU/L)	2459±1342.65	1033±589.61	<0.001****
INR	1.26±1.62	1.07±1.98	0.042*****

AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, *, **, ***, ****, *****: Significant

Table 5: Multivariate analysis of associated factors associated with para-aortic lymph node

Characteristic	OR	95% of CI		*P*
		Lower	Upper	
AST	0.999	0.998	1.001	0.482
ALT	1.001	0.999	1.002	0.599
ALP	1.002	1.001	1.004	0.010*
INR	2.397	000	70,895.811	0.868
Albumin	17.740	1.162	270.929	0.039**

AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, INR: International normalized ratio, CI: Confidence interval, OR: Odds ratio, *, **: Significant.

of malignant processes. Furthermore, there was a direct relationship between para-aortic lymphadenopathy and the levels of ALP and albumin. However, such lymphadenopathy did not significantly affect the hospital stay. On the other hand, Group C was significantly higher in albumin levels compared to Group D. This finding was quite unexpected because the levels of liver enzymes were higher in Group C compared to Group D. However, such finding is not reliable because albumin levels were checked upon admission and were expected to decline during hospitalization. Moreover, Group C included only three patients. Therefore, there was a high chance of laboratory error or incorrect recording of the laboratory test results.

Eventually, we concluded that the PHL had a significant relationship with the severity of hepatic inflammation in pediatric patients with hepatitis A. However, it seems that the disease severity was not affected by the hepatic decompensation because the PHL did not significantly affect the hospital stay or even the prognosis of the patients. Therefore, the main finding of the present study was the significant relationship between PHL and severity of hepatic inflammation in pediatric patients with hepatitis A, as well as the insignificant effect of such findings on the prognosis of these patients.

The present study had some limitations as well. First, we did not perform a follow-up ultrasound to assess the potential resolution of PHL due to financial limitations related to full clinical recovery and laboratory data. Moreover, considering the fact that hepatitis A has various differential diagnoses in the prodromal period, such as the common cold, we did not include the patients with a delayed presentation to the hospital in our study. Therefore, patients were divided based on the specific days before the onset of symptoms. Furthermore, our sample size was relatively small, and our statistical analysis would be more reliable if we had a large sample size of the HAV patients with para-aortic lymph nodes in ultrasound.

The present study indicated that ultrasound could be used in the diagnosis confirmation of hepatitis A. Moreover, it can have a supplementary role in the severity evaluation of hepatitis A in pediatric patients and ruling out the other causes of elevated liver enzymes.

Conclusion

The present study indicated that ultrasound could be used in the diagnosis confirmation of hepatitis A. Moreover, it can have a

supplementary role in the severity evaluation of hepatitis A in pediatric patients and ruling out the other causes of elevated liver enzymes.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that they are not financially or personally related to other people or organizations.

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