Prognostic value of gallbladder wall thickening in patients with acute hepatitis A

ULTRA SONO GRAPHY

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ORIGINAL ARTICLE

http://dx.doi.org/10.14366/usg.14052
pISSN: 2288-5919 • eISSN: 2288-5943
Ultrasonography 2015;34:139-143

Purpose: To investigate the clinical significance of gallbladder (GB) wall thickening frequently observed in patients with acute hepatitis A.

Methods: A total of 328 consecutive patients who were diagnosed with acute hepatitis A and underwent abdominal ultrasonography were enrolled retrospectively. Patients were divided into two groups: GB wall thickening (≥3 mm, group A) and no thickening (group B). Group A was subdivided into two subgroups (GB wall thickening of ≥10 mm, group A-1 and ≥3 mm to <10 mm, group A-2). The laboratory results related to liver function, hospitalization duration, and time to normalization of liver function were compared between the groups.

Results: A total of 230 patients showed GB wall thickening (group A). Besides gamma-glutamyl transpeptidase and alkaline phosphatase, all laboratory results of group A were significantly higher than those of group B ($P<0.05$). Compared with group B, the hospitalization duration and the time to normalization of liver function were significantly longer in group A ($P<0.05$). Group A-1 included 146 patients and group A-2 included 84 patients. No significant differences in laboratory results, hospitalization duration, and time to normalization of liver function were found between the two subgroups. In the multivariate logistic regression analysis, serum alanine transaminase, total bilirubin and albumin levels, and hospitalization duration were significantly associated with GB wall thickening in patients with hepatitis A.

Conclusion: The presence of GB wall thickening in patients with acute hepatitis A suggests a poorer prognosis irrespective of the degree of GB wall thickening or the degree of liver enzyme elevation.

Keywords: Hepatitis A; Liver function tests; Gallbladder; Ultrasonography

Received: November 4, 2014
Revised: December 23, 2014
Accepted: January 16, 2015

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How to cite this article:
Ahn JH, Chung JJ, Yu JS, Kim JH, Cho ES, Kim DJ. Prognostic value of gallbladder wall thickening in patients with acute hepatitis A. Ultrasonography. 2015 Apr;34(2):139-143.

Introduction

Tens of millions of hepatitis A virus infections occur each year worldwide [1], and the incidence of acute hepatitis A has been rapidly increasing in recent years. Gallbladder (GB) wall thickening is frequently observed in patients with acute hepatitis A [2–4]. Maresca et al. [4] identified GB abnormalities on ultrasonography (US) in 51% of consecutive patients presenting with acute hepatitis. In patients with acute viral hepatitis, thickening of the GB wall may be secondary to the inflammatory

process in the adjacent liver. Further, the severity of liver cell necrosis appears to influence the degree of GB wall thickening [5]. Several reports have established a connection between GB wall thickening and laboratory findings [4–6]; however, other investigators have found no association between GB wall thickening and laboratory findings [7,8]. In this study, we investigate the clinical significance of GB wall thickening on US in patients serologically confirmed with acute hepatitis A.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of our medical institution, with the waiver of informed consent. From March 2009 to December 2012, a total of 411 patients were diagnosed with acute hepatitis A at our institution on the basis of the results of hepatitis A virus-specific IgM antibodies in the blood and liver function tests, and abdominal US. Patients underwent blood tests at the time of admission, and on the same day or the next day, abdominal US was performed. Among these 411 patients, we excluded two patients who had a history of cholecystectomy, 76 patients for whom there was no follow-up liver function test, and five patients who had gallstones. In total, 328 consecutive patients (median age, 31.2 years; range, 3 to 53 years) were enrolled in the study.

Five radiologists with 5–20 years of experience in abdominal US performed US using an IU 22 (Phillips Medical Systems, Bothell, WA, USA) with a 1–4-MHz convex transducer and an Acuson Sequoia 512 (Acuson Corporation, Mountain View, CA, USA) with a 4-MHz convex transducer. Intercostal or longitudinal US scans were used to evaluate the GB wall thickness. Measurement of the GB wall thickness was performed by two abdominal radiologists who were unaware of the laboratory information of patients. Each reader measured the thickness of the GB wall (body portion of the GB) at a workstation (Centricity 2.0, GE Healthcare). Thereafter, the measured values obtained from the two readers were averaged, and the mean value was used. On the basis of previous studies, we considered the GB wall to be thickened in fasting subjects whenever its width exceeded 3 mm (Fig. 1) [4]. Patients were divided into the following two groups: patients with GB wall thickening (group A) and those without GB wall thickening (group B). The laboratory results of the patients with GB wall thickening were compared with those of patients without GB wall thickening. The tests included aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, direct bilirubin, albumin, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (γ-GT) levels; prothrombin time (PT); hospitalization duration; and time to normalization of liver function.

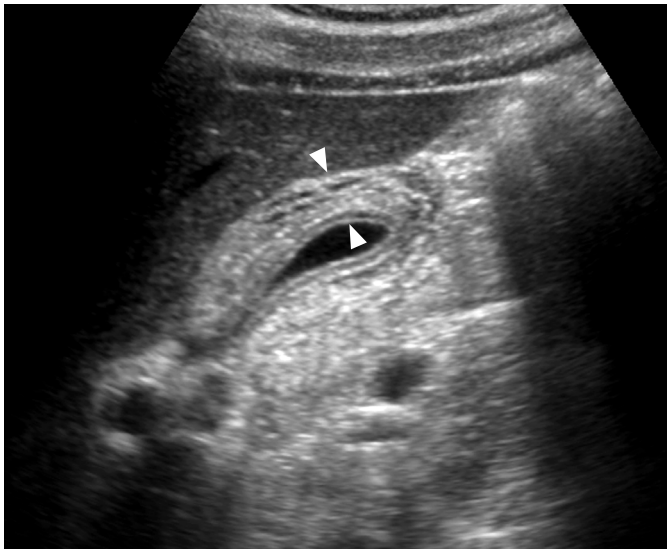

Fig. 1. **A 24-year-old male with acute hepatitis A.** Longitudinal sonogram of abdomen shows gallbladder wall thickening of about 12 mm (arrowheads).

Additionally, group A was subdivided into the following two subgroups (group A-1 and group A-2) for the comparison of laboratory results, hospitalization duration, and time to normalization of the liver function tests: GB wall thickness of 10 mm or more (group A-1) and GB wall thickness of less than 10 mm (≥3 mm to <10 mm, group A-2). Further, group B was subdivided into the following two subgroups (group B-1 and group B-2) for the comparison of hospitalization duration and time to normalization of liver function tests: patients with AST and ALT levels of 500 IU/L or more (group B-1) and patients with AST and ALT levels of less than 500 IU/L (group B-2). If the AST and ALT values were discordant, the higher of the two was used for classification.

We used the Mann-Whitney U test for a comparison of the continuous variables, and the data were expressed as median values and the interquartile range. The correlations between GB wall thickening and the variables were assessed using multivariate logistic regression analysis to identify the factors related to the GB wall thickening. On multivariate logistic regression analysis, we used the continuous variables that show a significant P-value on the Mann-Whitney U test. In addition, the variance inflation factor of total bilirubin and direct bilirubin is more than 10; therefore, we excluded direct bilirubin on the multivariate logistic regression analysis. Data were analyzed with statistical software SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA), and in all tests, a P-value of less than 0.05 was considered significant.

Results

Among the 328 patients, 230 patients (70.1%) showed GB wall thickening on US related to acute hepatitis A. The mean GB wall thickness was 8.04±3.96 mm. The mean AST, ALT, total bilirubin, direct bilirubin, and prolonged PT in group A were significantly higher than those in group B (98 patients, 29.9%). The mean albumin level in group A was significantly lower than that in group B. However, no significant differences were observed between the groups with respect to γ-GT or ALP (Table 1).

The hospitalization duration and time to normalization of liver function tests were 5.0 days (4.0–8.0 days) and 38.0 days (21.0–48.0 days) in group A and 5.0 days (3.0–6.3 days) and 24.5 days (15.0–45.5 days) in group B, respectively. Compared with group B, the hospitalization duration and time to normalization of liver function tests were significantly longer in group A (P<0.05). Among the patients with GB wall thickening, 146 patients (63.5%) had a GB wall thickness of 10 mm or more, and 84 patients (36.5%) had

Table 1. Clinical and laboratory findings for patients with and without GB wall thickening

Characteristic	Patients with GB wall thickening (group A, n=230)	Patients without GB wall thickening (group B, n=98)	P-value
Age (yr)	31.0 (3.0–53.0)	30.0 (7.0–45.0)	0.253
Laboratory data			
AST (IU/L)	2,435.0 (918.5–4,383.0)	1,200.5 (241.8–3,137.5)	<0.001
ALT (IU/L)	3,121.5 (1,841.8–4,594.5)	1,656.0 (686.0–3,174.5)	<0.001
Total bilirubin (mg/dL)	4.0 (2.7–6.0)	2.4 (1.3–4.1)	<0.001
Direct bilirubin (mg/dL)	2.9 (1.9–4.3)	1.8 (1.0–3.0)	<0.001
Albumin (IU/L)	4.0 (3.7–4.2)	4.2 (3.9–4.5)	<0.001
ALP (IU/L)	166.5 (134.0–215.8)	165.6 (124.8–226.3)	0.552
γ-GT (IU/L)	278.0 (193.0–386.0)	269.5 (184.5–437.0)	0.976
PT (INR)	1.3 (1.1–1.4)	1.1 (1.0–1.3)	<0.001
Hospitalization duration (day)	5.0 (4.0–8.0)	5.0 (3.0–6.3)	0.004
Time to normalization (day)	38.0 (21.0–48.0)	24.5 (15.0–45.5)	0.004

Values are presented as median (range).

GB, gallbladder; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio.

Table 2. Clinical and laboratory findings in patients with GB wall thicknesses of 10 mm or more and in patients with wall thicknesses of less than 10 mm (≥3 mm to <10 mm)

Characteristic	GB wall thickness of ≥10 mm (group A-1, n=146)	GB wall thickness of ≥3 mm to <10 mm (group A-2, n=84)	P-value
Age (yr)	32.0 (28.0–36.0)	31.0 (28.0–34.0)	0.248
Laboratory data			
AST (IU/L)	2,542.0 (1,143.0–4,510.0)	2,096.0 (321.0–4,374.0)	0.131
ALT (IU/L)	3,346.0 (2,179.0–4,710.0)	2,587.0 (1,104.0–4,497.0)	0.013
Total bilirubin (mg/dL)	4.0 (2.8–5.8)	3.8 (2.3–6.0)	0.699
Direct bilirubin (mg/dL)	3.0 (2.1–4.3)	2.9 (1.7–4.4)	0.535
Albumin (IU/L)	4.0 (3.7–4.2)	4.0 (3.7–4.3)	0.399
ALP (IU/L)	172.0 (140.0–216.8)	156.0 (131.0–215.5)	0.200
γ-GT (IU/L)	284.0 (193.0–398.0)	262.5 (194.8–379.5)	0.862
PT (INR)	1.3 (1.1–1.5)	1.2 (1.0–1.4)	0.011
Hospitalization duration (day)	5.0 (4.0–8.0)	6.0 (5.0–8.0)	0.163
Time to normalization (day)	41.0 (21.0–48.0)	32.0 (23.0–47.0)	0.359

Values are presented as median (range).

GB, gallbladder; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; γ-GT, gamma-glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio.

a GB wall thickness of less than 10 mm (≥3 mm to <10 mm). The mean ALT and prolonged PT in group A-1 were significantly higher than those of group A-2. However, no significant differences were observed between the two subgroups for other laboratory results, hospitalization duration, or time to normalization of liver function tests (Table 2).

In the multivariate logistic regression analysis, reduced albumin level (odds ratio, 0.275; 95% confidence interval [CI], 0.127 to 0.598; P=0.001), increased ALT level (odds ratio, 1.001; 95% CI, 1.000 to 1.001; P=0.002), increased total bilirubin level (odds ratio, 1.212; 95% CI, 1.081 to 1.360; P=0.001), and prolonged hospitalization duration (odds ratio, 1.133; 95% CI, 1.001 to 1.282; P=0.047) were significantly associated with GB wall thickening in patients with hepatitis A (Table 3).

Among the 98 patients in group B, 80 (81.6%) patients had AST or ALT levels of 500 IU/L or more. The mean hospitalization duration of the 80 patients was 5.0 days (3.0–7.0 days) and that of the other 18 patients was 4.5 days (2.8–6.0 days), a difference that was not significant (P=0.302). The mean time to normalization of liver function tests of the 80 patients was 33.0 days (19.3–48.8 days) and that of the other subgroup was 13.5 days (3.0–19.0 days) (P<0.001).

Table 3. Multivariate analysis of associated factors associated with GB wall thickening

Variable	Odds ratio	95% Confidence interval	P-value
AST	1.000	1.000–1.000	0.051
ALT	1.001	1.000–1.001	0.002
Total bilirubin	1.212	1.081–1.360	0.001
Albumin	0.275	0.127–0.598	0.001
PT	2.388	0.594–9.596	0.220
Hospitalization duration	1.133	1.001–1.282	0.047
Time to normalization	0.999	0.981–1.017	0.904

GB, gallbladder; AST, aspartate aminotransferase; ALT, alanine transaminase; PT, prothrombin time.

Discussion

GB wall thickening can be seen after a meal or after pharmacological stimulation, such as with cholecystokinin. Further, thickening of the GB wall may be observed in the case of acute and chronic cholecystitis, neoplasm, adenomyomatosis, obstructive jaundice, ascites, hypoalbuminemia, heart failure, and cirrhosis [4].

Inflammatory changes involving the GB may be observed in patients with clinical and laboratory findings of acute hepatitis, irrespective of the underlying cause. In the case of viral hepatitis, GB wall thickening is the most frequently observed pattern on US [4]. Moreover, the frequency of GB wall thickening is greater in patients with a viral infection than in patients with other potential causes of GB wall thickening [9]. In previous reports, the incidences of GB wall thickening in patients with acute hepatitis ranged from 51%–90% [4,6,7,9,10]. In our study, GB wall thickening was identified in 70.1% of the patients with acute hepatitis A.

Three hypotheses have been suggested to explain the mechanism of GB wall thickening in patients with acute hepatitis. One hypothesis is that hepatocyte injury causes temporary decreases in bile production and excretion [11–13]. The second hypothesis is that there is direct injury to and inflammation of the mucosal and muscular layers of the GB caused by hepatitis virus contained in the bile fluid [14–16]. The third hypothesis is that hepatocyte necrosis causes an inflammatory reaction in the tissues surrounding the liver, including the GB wall [2,5].

A direct correlation has also been reported between the levels of elevation of serum AST and ALT and GB wall thickening on US [2,4–6]. However, other studies have reported that the levels of serum AST and ALT are not related to GB wall thickening [7,8]. In our study, serum AST and ALT levels were significantly elevated in group A as compared to in group B. In addition, the bilirubin levels and the PT of group were significantly (P<0.001) higher than those of group B, suggesting that the GB may be somehow involved in the inflammatory process and that this involvement is closely related to the clinical course of acute hepatitis A. In fact, in our study, the hospitalization duration and time to normalization of liver function tests in group A were significantly longer than those in group B. Therefore, the US assessment of GB wall thickening may have prognostic value for patients with hepatitis A infection.

In our study, the degree of GB wall thickening was not correlated with the laboratory results (except ALT level and PT), hospitalization duration, or time to normalization of liver function tests. Further, 81.6% of the group B patients showed AST and ALT levels of 500 IU/L or more; no significant difference was observed in the hospitalization duration between patients divided into subgroups according to the AST and ALT levels. These findings suggest that neither the degree of GB wall thickening nor laboratory results are closely correlated with the prognosis in patients with acute hepatitis A.

This study has several limitations because of its retrospective design. First, no follow-up US was conducted to assess for the recovery of GB wall thickening. Second, laboratory follow-up was performed at an outpatient clinic within 15–30 days after discharge; therefore, the time to normalization of liver function tests may be inaccurate. In addition, we excluded 76 patients for whom there were no follow-up liver function tests, and the exclusion of these patients may well bias the results of the time to normalization of

liver function tests. Third, the measurement of GB wall thickness may not have been consistent because many different physicians performed the US assessments in this retrospective study.

In conclusion, the presence of GB wall thickening in patients with acute hepatitis A suggests a poorer prognosis irrespective of the degree of wall thickening or the degree of liver enzyme elevation.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported in part by the Research Fund of the Korean Society of Ultrasound in Medicine.

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