Ascites and Gallbladder Abnormalities are Frequent Findings in Adults with Hepatitis A Virus Infection

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ABSTRACT: **Background:** Since the implementation in Israel in 1999 of a hepatitis A virus (HAV) immunization program for children, HAV infections in the country have occurred mostly in adults. HAV infection in adults is usually symptomatic and may present with hepatic as well as extrahepatic abdominal complications.

Objectives: To estimate the prevalence of extrahepatic abdominal complications in patients diagnosed with HAV.

Methods: Most extrahepatic abdominal complications corresponding to HAV infection have ultrasonographic manifestations; therefore, we retrospectively collected findings from ultrasound examinations in addition to laboratory data from adult patients with HAV infection who were admitted to our medical center between 2004 and 2016. Associations between ultrasonographic findings and laboratory parameters that reflect disease severity were identified.

Results: A total of 43 consecutive adult patients were included in this study. None presented with fulminant hepatic failure. Thirty patients (70%) had at least one ultrasonographic finding. Ascites was noted in 8 patients, a thickened gallbladder wall was observed in 14, pericholecystic fluid was found in 8, and biliary sludge was observed in 4. Significant associations included the presence of any ultrasonographic finding and peak total bilirubin levels ($P = 0.021$), the presence of ascites with peak aspartate and alanine aminotransferase levels ($P = 0.041$ and $P = 0.038$, respectively), and the presence of biliary sludge and nadir albumin during the HAV disease course ($P = 0.037$).

Conclusions: Abdominal ultrasonographic findings, such as ascites and gallbladder abnormalities, are frequently observed during acute HAV infection and are significantly associated with disease severity.

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KEY WORDS: ascites, gallbladder abnormalities, hepatitis A infection (HAV), abdominal ultrasound

The clinical spectrum of hepatitis A virus (HAV) infection ranges from asymptomatic infection to fulminant hepatitis. Disease severity may correlate with the age of the host [1]. Since 1999, after Israel implemented a national immunization program for children, HAV infection in Israel has occured mostly in adults [2]. HAV infection in adults is usually symptomatic and may present with hepatic as well as extrahepatic (abdominal and extra-abdominal) complications, such as acute kidney injury, autoimmune hemolytic anemia, pleural or pericardial effusion, acute pancreatitis, acute reactive arthritis, or neurological complications [3].

Involvement of extrahepatic organs with acute infection by one of the hepatotrophic viruses (HAV, hepatitis B, hepatitis C, hepatitis E, cytomegalovirus, and Epstein–Barr virus) has been reported previously [4,5]. However, despite HAV being the most frequent cause of acute viral hepatitis in many parts of the world, few studies report extrahepatic (mainly intra-abdominal) manifestations of this virus. In this study, we report abdominal ultrasonographic findings observed in adult patients with HAV infection. Most of these findings correlated with disease severity.

PATIENTS AND METHODS

This retrospective observational study was conducted at the two Jerusalem hospitals that are part of the Hadassah–Hebrew University Medical Center. The participating hospitals serve as primary, secondary, and tertiary medical care facilities for the Jewish and Arab (mainly Muslim) population of Jerusalem. Included in this study were adult patients (> 18 years old) who were admitted to one of the medical center campuses between April 2004 and July 2016 due to symptomatic acute HAV infection.

Clinical, biochemical, serological, and imaging data of the patients included in the study were collected retrospectively from the patients' electronic medical records. Acute HAV infection was identified by a combination of the appropriate clinical scenario, acute elevation of hepatic aminotransferase level to more than double the upper limit of normal values, presence of positive anti-HAV immunoglobulin M serology (Abbott Diagnostics, USA), and the absence of other etiologies for acute liver injury. Additional laboratory parameters, including blood cell counts, liver enzyme activity (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT]), levels of bilirubin, creatinine, urea, albumin, and prothrombin time, were mea-

sured using standard automated procedures. During the study period, laboratory tests were performed by the same on-site laboratory facilities, using identical kits.

All patients included in this study underwent abdominal ultrasound evaluation using a scanner equipped with a 2.6 MHz convex probe or a 1.5-4 convex probe (vendors in our institution are Siemens [Germany] or Philips [Netherlands]). All ultrasound studies were conducted by experienced operators (specialized and experienced technicians and/or radiologists) and were reviewed by two expert radiologists (at the time of the exam and retrospectively, during data collection for this study). Findings reported include spleen size, presence of pericholecystic fluid, ascites, abdominal lymphadenopathy, and ultrasonographic Murphy's sign (defined as focal tenderness provoked by direct pressure over the gallbladder by the sonographer). Changes in gallbladder morphology (shape, wall thickness, and content) were reported when gallbladder was present.

Numerical data variables are presented as median (interquartile range) unless stated otherwise. The Wilcoxon signed-rank test was used to detect association between ultrasonographic findings and the various laboratory parameters measured. In all tests, $P < 0.05$ was considered significant. Statistical analysis was performed using R statistical software version 3.3.3

This study was approved by the institutional review board and ethics committee for the protection of human subjects, who waived the requirement for informed consent as this study is based on de-identified data that were collected retrospectively.

RESULTS

During the study period, 73 adult patients with acute HAV infection were admitted to our medical center. Patients with concomitant infection with chronic hepatitis C, chronic hepatitis B, acute Epstein–Barr virus infection (5 patients); or non-alcoholic fatty liver disease (2 patients); or chronic biliary tract disease (1 patient) were excluded. Among the remaining 65 patients, only 43 patients underwent ultrasonographic examination of the liver and abdomen. The decision to perform an ultrasound examination during hospitalization was made by several different physicians assigned to the care of patients within the departments of medicine at both medical campuses. At that time, no research was envisioned.

The mean age of the patients was 27.8 ± 11.7 years (range 18–66 years). Twenty-three patients (53.5%) were male and 27 (62.8%) where Arab. The mean hospitalization duration was 4.6 ± 1.8 days (median 4 days). Table 1 summarizes laboratory results that were obtained during the hospital course in the study population.

Ultrasonographic findings for these patients are described in Table 2. Most patients (30 of 43, 69.8%) had at least one finding. Ascites was present in eight patients (18.6%, 6 females and 2 males). In seven patients the amount of ascites was estimated to be mild and in one moderate [Figure 1A]. Two patients underwent cholecystectomy prior to the occurrence of HAV infection. Gallbladder wall thickening was reported in 14 of 41 patients (34.2%). The mean gallbladder wall width was 5.83 ± 1.87 mm, median 5 mm. One patient had gallbladder dilatation (2.4%). Pericholecystic fluid was reported in eight patients (19.5%) [Figure 1B], biliary sludge was noted in four patients (9.8%), and sonographic Murphy sign was observed in two patients (4.9%). Periportal edema was noticed in three patients (7.0%). Signs of intrahepatic or extrahepatic bile duct dilatation or of obvious gallbladder stones were not found in any patient.

Splenomegaly was observed in 17 patients (40.5%). One patient underwent splenectomy prior to the occurrence of

Table 1. Laboratory tests: peak and nadir values observed during the hospital course (n=43)

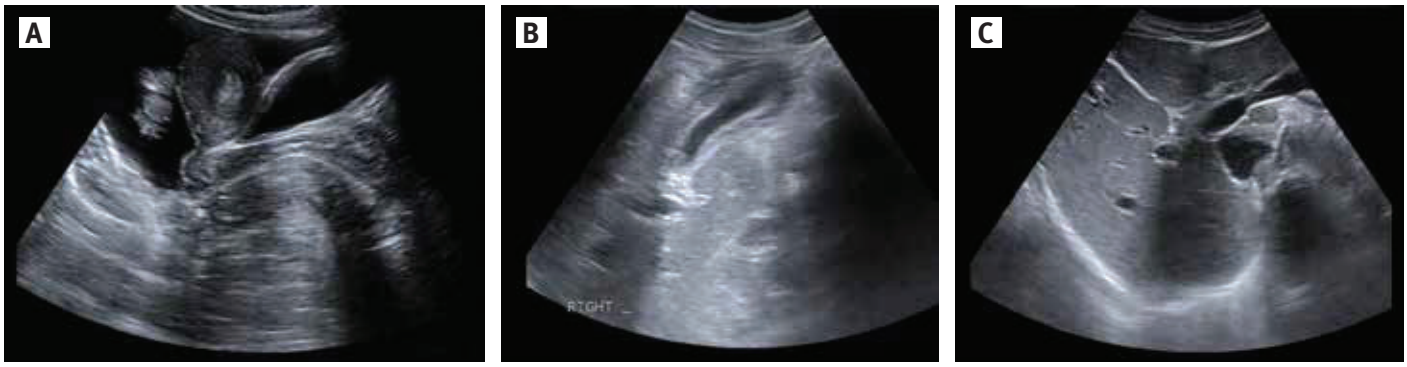
Laboratory test	Type	Median value (interquartile range)
Prothrombin time (international normalized ratio)	Peak	1.34 (1.23–1.6)
Alanine aminotransferase (U/L) level	Peak	2672 (1628–3674)
Aspartate aminotransferase (U/L) level	Peak	1650 (874–2577)
Gamma-glutamyl transferase (U/L) level	Peak	265 (158–349)
Alkaline phosphatase (U/L) level	Peak	234 (176–307)
Lactate dehydrogenase (U/L) level	Peak	1350 (596–2851)
Albumin (g/L) level	Nadir	33 (30–36)
Total bilirubin (μmol/L) level	Peak	140 (99–177)
White blood cell count (10^3 cells/μl)	Nadir	4.6 (3.9–5.9)
Hemoglobin level (g/dl)	Nadir	13.3 (11.7–14.5)
Platelet count (10^9/L)	Nadir	194 (147–257)

Table 2. Ultrasonographic findings

Ultrasound finding	No. of patients*	Percentage (%)
Any abdominal ultrasound finding	30/43	69.8
Splenomegaly	17/42	40.5
Thickened gallbladder wall	14/41	34.2
Pericholecystic fluid	8/41	19.5
Biliary sludge	4/41	9.8
Sonographic Murphy sign	2/41	4.9
Gallbladder dilatation	1/41	2.4
Ascites	8/43	18.6
Lymphadenopathy	3/43	7.0
Periportal edema	3/43	7.0

*Two patients underwent cholecystectomy and one patient underwent splenectomy before their hospitalization for hepatitis A infection

Figure 1. Ultrasound images
[A] A 25 year old female with mild to moderate amount of pelvic free fluid, **[B]** A 35 year old male showing a non-distended gallbladder with marked wall thickening, edematous wall and a minimal amount of pericholecystic fluid, **[C]** A patient with lymph nodes measuring up to 1.5 cm in the porta hepatis



HAV infection. The mean spleen size was 14.0 cm ± 1.2 cm. Abdominal lymphadenopathy was observed in three patients (7.0%): in the porta hepatis for two patients [Figure 1C] and retroperitoneal (behind the head of pancreas) in one. Doppler examination of the hepatic and portal veins was performed in 11 of 43 patients, and no anomalies in the hepatic and portal veins circulation were detected.

We assessed whether the presence of ultrasonographic findings correlated with disease severity by testing for statistical associations with known laboratory parameters of disease severity using the Wilcoxon signed-rank test. Associations were statistically significant only for the following parameters: any ultrasound finding and peak bilirubin levels ($P = 0.021$), presence of ascites and peak AST and ALT levels ($P = 0.041$ and $P = 0.038$, respectively), and presence of biliary sludge and the nadir albumin levels ($P = 0.037$).

Albumin levels did not correlate with the presence of any other ultrasonographic findings. Information regarding follow-up ultrasound examinations, performed after hospital discharge in any of the patients from the present cohort, was not available.

DISCUSSION

HAV infection is the most common cause of acute viral hepatitis worldwide. In recent years, a substantial decline in the incidence of HAV infection, mainly in the pediatric population, has been observed. This result is mostly due to the implementation of vaccination programs and improvements in living and sanitation conditions in all age groups [6]. However, despite a dramatic decrease of HAV infection in the pediatric population, outbreaks of HAV infection still occur, especially among non-vaccinated adolescents and adults [7]. While HAV infection in children is almost asymptomatic or mild, HAV infection in adults may manifest into severe hepatitis with or without various extrahepatic complications and may even deteriorate to acute liver failure [6].

In our cohort of adult HAV patients who underwent ultrasound examination of the abdomen, most were found to have at least one ultrasonographic finding. These findings included ascites, a variety of gallbladder changes (including gallbladder wall thickening, pericholecystic fluid, biliary sludge, and gallbladder dilatation), splenomegaly, periportal edema, and abdominal lymphadenopathy.

The presence of ascites in eight HAV adult patients is a novel finding. Ascites during the course of HAV was reported previously only in a few case reports, and mainly among pediatric patients [8-11]. The etiology of ascites in patients with HAV infection is unknown. In patients with acute hepatitis B, two types of ascites have been observed: a transudative type of ascites with low protein content and no leukocytes in the ascitic fluid, and an exudative type of ascites with high protein content and an increased number of lymphocytes. Patients with transudative ascites commonly presented with severe hepatic failure. The presence of ascites was considered to be caused by an increased portal hypertension due to distortion of the liver architecture and liver cell dropout [12,13]. However, exudative ascites was considered to be the consequence of either a direct invasion of the peritoneum by the virus or secondary to an immunologic process that was mediated by immune complexes and complement. The prognosis of the patients with exudative ascites was good, and the ascites disappeared with the improvement of the acute liver injury [12-14]. All our HAV patients recovered and none developed fulminant hepatic failure. Therefore, despite the fact that no examination of ascitic fluid was performed in any of the patients, we may assume that the ascites in these patients had the characteristics of the exudative type.

Of note, two of the eight patients with ascites, and an additional nine patients (of 35 patients without ascites) underwent a Doppler sonography of the hepatic and portal veins during their hospital course. This imaging modality allowed detection of disturbances in the flow of either the portal or hepatic veins, which in patients with HAV may indicate the

presence of severe liver disease and the impending development of portal hypertension [13,15]. Among the 11 patients who underwent Doppler sonography, none had detectable impairment of flow, supporting the assumption that ascites was the exudative type and not the transudative type.

More than one-third of our patients had gallbladder thickening. The presence of gallbladder thickening as well as other ultrasonographic findings was associated with the degree of liver dysfunction, as measured by peak total bilirubin levels. Gallbladder wall thickening (> 3.5 mm) in patients with HAV infection was reported previously [15-20]. Suk et al. [20] examined 232 patients with acute hepatitis (from various etiologies) and found gallbladder wall thickening in 63% of their patients. In that study, presence of gallbladder wall thickening was associated with HAV infection, female gender, and increased total bilirubin levels. The reported incidence of gallbladder thickening in patients with HAV infection is diverse and ranges from 33.3% [17] to 70.1% [16]. Compared to HAV patients without gallbladder thickening, HAV patients with gallbladder thickening presented with higher ALT and AST levels, higher degrees of liver dysfunction (as measured by total bilirubin levels, lower serum albumin levels, and prolongation of the prothrombin time). In addition, a longer duration of hospitalization and a longer recovery period until liver function tests were normalized were noted [16]. The poorer prognosis of patients with gallbladder thickening was not related to the degree of gallbladder wall thickening or to the degree of liver enzyme elevation [16].

The presence of gallbladder thickening in patients with HAV is not unique and was reported in other infectious diseases, such as Q fever [21], Dengue infection [22], and Epstein–Barr virus [23]. The cause of gallbladder wall thickening in patients with HAV and the other infectious diseases is unclear. Several mechanisms were hypothesized: direct injury to the mucosal and muscular layers of the gallbladder by HAV RNA [24], decreased bile production and excretion due to hepatocyte injury [16], reactive inflammation in organs adjacent to the inflamed liver [16,25], and capillary leakage and hypoproteinemia [22]. Interestingly, in Dengue infection the existence of gallbladder thickening and of ascites is common [22].

In four of our patients, biliary sludge was detected. This finding was also reported by others [18,19]. The occurrence of biliary sludge may be related to decreased bile production and flow caused by hepatocyte damage and impaired biliary motility due to gallbladder wall thickness. It is thought to be transient [19].

Our study has several limitations. First, it is retrospective, and, as such, is subjected to selection bias. Second, it includes only hospitalized patients and does not include adults with HAV infection who might not have been diagnosed or who were treated in an outpatient setting. Thus, this study evaluated the clinical course of HAV infection in hospitalized patients; however, it did not assess the true incidence of extrahepatic, abdominal complications of HAV infection in adults. The policy at our medical center is to admit every adult who presents to the emergency departments with acute liver injury. Thus, we believe that our patient group included the majority of adults with HAV infection in our community during the study period. Third, treatment provided to HAV patients was not standardized and their care was determined by different physicians during the course of their hospitalization. In particular, the decision whether to perform an ultrasonographic examination was likely to be affected by the clinical approach of the treating physicians and the course of the disease. HAV patients who appeared sicker were therefore more likely to be included in this cohort. Last, laboratory tests and ultrasonographic studies were performed at different times during the disease and no follow-up ultrasound studies were performed. These differences could have impacted the results since changes detected in HAV patients by abdominal ultrasound are usually transient and may vary during the course of the disease [19].

CONCLUSIONS

Our study shows that adult HAV infection frequently involves, in addition to the liver itself, other abdominal organs including the peritoneum and gallbladder. Moreover, this extrahepatic involvement is a marker for disease severity. Physicians caring for adults with HAV infection should be aware that such disease manifestations may occur, and they should be familiar with their clinical course to provide proper medical treatment and avoid unnecessary clinical investigations.

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Capsule

RNA treats preeclampsia

Small interfering RNAs (siRNAs) bound to cholesterol can be non-selectively taken up by a range of tissues with high blood flow and porous (fenestrated) endothelium. **Turanov** and colleagues showed that such hydrophobic siRNA accumulates in the placenta, which offers possibilities for a range of therapies for pregnancy-related diseases. Preeclampsia is a pregnancy disorder caused by a circulating tyrosine kinase called sFLT1. This kinase inhibits blood vessel formation in the placenta, thus risking damage to the pregnancy. Placenta-originated sFLT1 has a different sequence than FTL1 in other tissues, which means an siRNA can be designed to selectively silence it. This approach was tested in both mouse and baboon preeclampsia models.

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Capsule

The risk of gout among patients with sleep apnea: a matched cohort study

Obstructive sleep apnea (OSA) is associated with a range of serious co-morbidities. **Blagojevic-Bucknall** investigated whether people with OSA are more likely to develop gout, in the short and long term, compared to those without OSA. A matched retrospective cohort study was undertaken using the UK Clinical Practice Research Datalink. Individuals aged ≥ 18 years who received a diagnosis of OSA between 1990 and 2010 were identified and matched in age, gender, and practice with up to four individuals without OSA. Follow-up continued until the end of 2015. Hazard ratios (HRs) were estimated using Cox regression adjusted for general health, lifestyle, and co-morbidity characteristics. The risk of developing gout was assessed at different time points, and the body mass index (BMI) category-specific results were presented. The study sample included 15,879 patients with OSA and 63,296 without. The median follow-up was 5.8 years. The authors found that 4.9% of patients with OSA and 2.6% of patients without the disorder developed gout. The incidence rate per 1000 person-years was 7.83 (95% confidence interval [95%CI] 7.29–8.40) and 4.03 (95%CI 3.84–4.23) among those with and without OSA, respectively. The adjusted HR was 1.42 (95%CI 1.29–1.56). The risk of developing gout among OSA patients compared to those without was highest 1–2 years after the index date (HR 1.64, 95%CI 1.30–2.06). This finding persisted among those who were overweight and obese. For those with normal BMI, the highest significant HR (2.02, 95%CI 1.13–3.62) was observed at 2 to 5 years after the index date.

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