Pediatric hepatitis A from ultrasonographic, immunologic, and other points of view

Zaher G. Ewadh¹, Basim A. Abd²*, Hassan F. Al-Khafaji³

¹ FICMS (Pediatrics), Babylon Health Directorate/Iraq
² PhD, Lecturer (Medical Physiology), College of Medicine, University of Babylon/Iraq
³ CABR (Radiology), Babylon Health Directorate/Iraq

*Corresponding author:
Basim A. Abd
basim6mol@gmail.com

Abstract

Background and objective: Viral hepatitis A infection is ordinarily a rapid and is usually a self-limited disease of the liver caused by hepatitis A virus that is transmitted enterically. One of its complications is acute acalculous cholecystitis. This work aims to prove the impact of pediatric hepatitis A viral infection on the thickness of gall bladder wall, and on some other hematological, immunological and biochemical parameters. Materials and Methods: This is a cross-sectional study conducted on 94 pediatric patients infected with hepatitis A; who were admitted to the isolation unit of Babylon Maternity and Pediatric Hospital in Hilla City, Babylon Governorate-Iraq, over a period from the beginning of September 2018 to the end of October 2019. The patients were divided into 2 groups, based on the thickness of their gallbladder (GB) wall as determined by the use of ultrasonography. The first group (29 patients) represents patients with normal GB wall (less than 3mm thick), and the second group (65 patients) represents those with thick wall (3mm and more). Demographic data (age and gender) were addressed for all the patients, then, a blood sample was drawn from each one of them for subsequent analyses. Results: Statistically significant differences were found between the study groups regarding age ($p = 0.047$), gender ($p= 0.001$), the distribution of positive and negative immunoglobulin M (IgM) ($p= 0.0001$), the presence or absence of splenomegaly ($p= 0.049$), prothrombin time (PT) ($p= 0.0001$), all liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP))(for all of them, $p= 0.0001$), in addition to the total serum bilirubin (TSB)($p= 0.0001$). On the other hand, no statistically significant difference was found regarding the presence or absence of hepatomegaly ($p = 0.985$). Conclusion: From the present study, we can conclude that pediatric hepatitis A virus infection has a positive impact on the thickening of the GB wall and can cause alterations in different immunological, hematological and biochemical parameters.

Keywords: Hepatitis A, gall bladder, liver enzymes.

Introduction

Hepatitis virus type A (HAV), is a ribonucleic acid (RNA) virus that has a feco-oral mode of transmission and linked closely to deprived hygiene and low sanitation. Its transmission is primarily caused by close contact with unhealthy persons resulting in liver infection with its inflammation (1). Underdeveloped countries showing a high rate of endemicity due to their very poor health, hygiene and sanitations, such as drinking and eating contaminated water and food (2). The symptomatic HAV infection incidence rate is approximately 1.3 million people per year over the world; symptoms of acute disease are nonspecific and widely variable, mostly presented as fever, malaise, and jaundice (3,4).

A normal wall of gallbladder looks as a pencil-thin echogenic line on scanning with ultrasound (US). This thin wall could show an increment in thickness under several conditions, even though this wall thickness rarely exceeds 3 mm in these cases. Diffuse increment of GB wall thickness could be happening in patients whose GB is involved secondary to extrinsic pathologic condition but not due to a primary GB disease. The thickening causes of GB wall could be determined by comparing the imaging findings with the clinical presentations in most cases (5).

Acute acalculous cholecystitis (AAC) is one of the children diseases, ~30-50% of acute children cases of cholecystitis are the acalculous form. Its diagnosis is difficult in spite of the applications of variable laboratory and clinical diagnostic procedures; also, the accuracy of several imaging diagnostic techniques has not been proven (6). HAV infection with its related cholecystitis may be attributed to the invasion of the infectious agents and its pathological effects to GB and bile duct epithelium with the CMI response, such pathological effects are local extension of the hepatic inflammatory process, hypoalbuminemia, and elevated portal pressure; these parameters could be cooperatively initiating edema of the GB wall. The diagnosis can be suspected clinically then confirming the diagnosis through ultrasound (7). The ultrasonographic features for AAC diagnosis including (1) Distention of GB; (2) GB wall thickening (>3mm); (3) No acoustic shadow or biliary sludge; (4) Accumulation of perivesical liquid and (5) No dilatation of the extra and intrahepatic bile ducts (8).

This work aims to prove the impact of pediatric hepatitis A viral infection on the thickness of gall bladder wall, and on some other hematological, immunological and biochemical parameters.

Materials and methods

This is a cross-sectional study conducted on 94 pediatric patients infected with hepatitis A; who were admitted to the isolation unit of Babylon Maternity and Pediatric Hospital in Hilla City, Babylon Governorate-Iraq, over a period from the beginning of September 2018 to the end of October 2019. The patients were divided into 2 groups, based on the thickness of their GB wall as determined by the use of ultrasonography. The first group (29 patients) represents patients with normal GB wall (less than 3mm thick), and the second group (65 patients) represents those with thick wall (3mm and more).
Demographic data (age and gender) were addressed for all the patients, then, a blood sample was drawn from each one of them for subsequent analyses.

**Blood collection and serum preparation**

Three milliliter of fresh blood was drawn at 9:00 am from both groups of participants. Two types of labeled tubes were used; the first one contains ethylenediaminetetra-acetic acid (EDTA) as an anticoagulant to prevent clotting of blood to be used for hematological studies; the second type of tubes was without anticoagulant as gel tubes, for preparing sera by putting blood in the tubes and allowing it to clot for 15-30 min, then separating it by centrifugation for 10 min at 3000 round per minute to be used in the subsequent biochemical tests (9). Each sample was labeled and given a serial number together with the participant’s name. Serum samples were kept frozen at −20°C for subsequent immunological and biochemical analyses.

**Hematological parameters**

Prothrombin time was done by the use of Owren PT method (10).

**Immunological parameters**

Immunoglobulin M antibodies that are HAV-specific were determined in the serum by the aid of an enzyme-linked immunosorbent assay (ELISA) kit (Limiquick, USA). The levels of these antibodies were considered to be positive if they were greater than the determined cutoff point.

**Biochemical parameters**

Alanine aminotransferase, AST and ALP estimation was done by the use of their ELISA kits (Randox, UK). Total serum bilirubin was done by the use of its ELISA kit (Biolabo, France).

**Statistical analysis**

Numerical parameters were represented as mean ± standard deviation (SD), while the other categorical parameters were stated as percentages (no. (%)). The two sets of participants were compared using independent samples t-test for the numeric parameters and chi-square test for the categorical parameters. All analyses were done by the use of a statistical package of social science (SPSS) computer program (Chicago, IL, USA). P value that is less than 0.05 was addressed to be significant statistically (11).

**Results**

Table (1) demonstrates the age distribution for the two patients' groups. The mean of age for the first group of patients (with normal GB wall) was (6.69±2.85) years with a range between (2-11) years, while the mean age for the second group of patients (with thick GB wall) was (5.58±2.27) years with a range between (2-12) years. A statistically significant difference was present between the two sets of patients regarding age (p value = 0.047).
Table (1) Age distribution for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Age (years) Mean ± SD</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.69±2.85</td>
<td>5.58±2.27</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Table (2) shows the gender distribution for the study groups. Twenty-one males and 8 females were present among the first group; while the second group contains 23 males and 42 females. Again, a significant statistical difference was present between the study subjects regarding gender distribution (p value = 0.001).

Table (2) Gender distribution for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group 1 (Normal GB wall)</th>
<th>Group 2 (Thick GB wall)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>21 (72.4)</td>
<td>23 (35.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Females</td>
<td>8 (27.6)</td>
<td>42 (64.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
<td>65 (100)</td>
<td>94 (100)</td>
</tr>
</tbody>
</table>

The distributions of positive and negative immunoglobulin M and the presence or absence of splenomegaly for the two groups of patients are shown in tables (3) and (4), both had a significant statistical difference between the two sets of patients (p values = 0.0001 and 0.049, respectively). On the other hand, no significant difference was found between the two groups of study regarding the presence or absence of hepatomegaly (p value = 0.985), as described in table (5) below.

Table (3) Positive and negative immunoglobulin M distribution for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>IgM</th>
<th>Group 1 (Normal GB wall)</th>
<th>Group 2 (Thick GB wall)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>4 (13.8)</td>
<td>63 (96.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative</td>
<td>25 (86.2)</td>
<td>2 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
<td>65 (100)</td>
<td>94 (100)</td>
</tr>
</tbody>
</table>

- GB: Gall bladder. - SD: Standard deviation.

- IgM: Immunoglobulin M.- GB: Gall bladder.
Table (4) Distribution of splenomegaly for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall)</th>
<th>Group 2 (Thick GB wall)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM Present No. (%)</td>
<td>3 (10.3)</td>
<td>18 (27.7)</td>
<td>0.049</td>
</tr>
<tr>
<td>SM Absent No. (%)</td>
<td>26 (89.7)</td>
<td>47 (72.3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
<td>65 (100)</td>
<td>94 (100)</td>
</tr>
</tbody>
</table>

- SM: Splenomegaly.- GB: Gall bladder.

Table (5) Distribution of hepatomegaly for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall)</th>
<th>Group 2 (Thick GB wall)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM Present No. (%)</td>
<td>16 (55.2)</td>
<td>36 (55.4)</td>
<td>0.985</td>
</tr>
<tr>
<td>HM Absent No. (%)</td>
<td>13 (44.8)</td>
<td>29 (44.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>29 (100)</td>
<td>65 (100)</td>
<td>94 (100)</td>
</tr>
</tbody>
</table>

- HM: Hepatomegaly.- GB: Gall bladder.

The values of biochemical parameters (ALT, AST, ALP and TSB) are shown in tables (6), (7), (8) and (9), respectively, all displaying a significant statistical difference between the two sets of patients (for all of them, \( p \) value = 0.0001). Also, the values of prothrombin time (table 10) showed a statistically significant difference between the two patients' sets (\( p \) value = 0.0001).

Table (6) Values of alanine aminotransferase for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (u/L) Mean ± SD</td>
<td>663.79±229.22</td>
<td>1143.63±300.32</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

- ALT: Alanine aminotransferase.- GB: Gall bladder.- SD: Standard deviation.

Table (7) Values of aspartate aminotransferase for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (u/L) Mean ± SD</td>
<td>386.34±160.07</td>
<td>959.52±177.03</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table (8) Values of alkaline phosphatase for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP (u/L) Mean ± SD</td>
<td>363.24±126.19</td>
<td>857.80±128.73</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


Table (9) Values of total serum bilirubin for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSB (mg/dl) Mean ± SD</td>
<td>1.676±0.57</td>
<td>4.329±1.70</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

- TSB: Total serum bilirubin.- GB: Gall bladder.- SD: Standard deviation.

Table (10) Values of prothrombin time for the two groups of patients with hepatitis A.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Normal GB wall) (n=29)</th>
<th>Group 2 (Thick GB wall) (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (seconds) Mean ± SD</td>
<td>11.38±0.94</td>
<td>17.03±3.30</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


Discussion

HAV infection prevalence in children under 5 years of age could be reached 100%. Its acquisition in the developing countries can occur very early in child's life and nearly most of adults having detectable anti-HAV levels, thus they are immunized to infection (12). Certain work at Babylon Province/Iraq concerning with the frequency distribution of HAV in relation with different demographic parameters; showing that there were highly significant differences in relation with residence, age, personal hygiene and family history among children with age group less than 5 years in comparison with those older than 5 years; while there were no differences regarding gender (13). Moreover, Rafeey and Shoaran (14) showed no differences concerning sex and age, similar results were also obtained in two separated works in Zanjan and Isfahan (Iran) on pediatric cases, where they instituted that there were no associations between age, sex and the seropositivity in the first work and between sex and positive antibodies in the second survey (15,16).

Different Iraqi researchers studied the positivity of anti-HAV antibodies among populations. The anti-HAV antibodies positivity were the lowest in Al-Ta’nim, Dahuk, Al-Basrah and Diyala with a frequency range 85.2-95% (17). Closely related research was performed in Egypt with frequency distribution of anti-HAV antibodies was 86.2% (18).

Acute acalculous cholecystitis is the inflammation of the gallbladder without evidence of calculi that is frequently allied with empyema, edema, gangrenes and perforations, and it is associated with high morbidity and mortality; GB inflammatory changes might be detected in patients with laboratory and
clinical presentations of acute hepatitis, irrespective of the underlying cause. These changes are most frequently assumed reactive and attributed to adjacent hepatic inflammation (19).

Furthermore, evidence of GB wall thickening is much more noticeable in patients with a viral infection as HAV infection than in those with other impending causes related to GB wall thickening. Three suggestions have been recommended to describe the mechanism of GB wall thickening among patients with acute hepatitis. The first one showed that injuries to hepatocytes causing temporary decrements in bile production and its excretion. The second mechanism proposing that inflammation and direct injuries to the muscular and mucosal layers of GB caused by hepatitis virus presented in the bile fluid. The last theory is that necrosis of the hepatocytes causing an inflammation of tissues surrounding the liver, including GB wall (20,21).

Approximately 51-90% of patients with acute hepatitis were associated with GB wall thickening, and the commonest cause of acute hepatitis was viral hepatitis especially HAV as 83% by two separated studies (20,22) and proposing that there were prominent changes in the serosal and muscular layers. These groups also showing highly elevated levels of serum liver enzymes when compared with those of normal GB wall.

Surgical causes of obstructive jaundice should be excluded, this can be performed by ultrasonography, while acute hepatitis especially the viral one can be proposed by obtaining liver enlargement with diffuse increments of echogenicity of portal triads, liver texture may seem normal (23,24).

HAV infection has a special criterion when compared with hepatitis B and C, as it doesn't progress into chronic infection. Its symptoms are variable and nonspecific, including nausea, malaise, fever, jaundice, and anorexia, its incubation period is 28 days and its diagnosis is established by the positivity for HAV-specific IgM antibodies in blood (25,26).

Inflammation, necrosis of hepatic cells with many changes in the GB wall in correlations with increments of liver enzymes and serum bilirubin all these factors could be concomitantly linked to increase GB wall thickness (27,28). Ahn and his colleagues (21) revealed that the mean ALT, AST, TSB and prolonged PT among group with GB wall thickening were significantly different and higher when compared with those with normal GB wall; proposing that there may be an involvement of GB during the clinical course of acute HAV infection, resulting in thickening of its wall.

There is a close relationship between patients' age with the possibility and degree of symptomatic illnesses from HAV infection. As young children, ≥ 6 years of age who have hepatitis A are often asymptomatic or simply they manifesting signs and symptoms of viral gastroenteritis without jaundice. While those children <6 years of age, nearly 70% of all infections are asymptomatic. Regarding older children and adults, their infections are generally symptomatic, with prominent jaundice in more than 70% of cases; yielding a fulminant hepatitis A (29). Significantly, 80% of symptomatic patients in older children having hepatomegaly, whereas, fewer consequences as arthritis, leukocytodlastic vasculitis, cervical lymphadenopathy, splenomegaly and rarely, evanescent rash (30).

Acute hepatic failure is seldom need hospitalization. Hepatic injury is suggested when (INR> 1.5 and/ or PT> 15 with encephalopathy, or INR> 2.0 and/ or PT> 20 ± encephalopathy). These procedures must be applied within 8 weeks after the onset of the disease, and the above-described coagulopathy (prolonged prothrombin time and/ or INR) who is not responding to treatment with vitamin K, where
more aggressive supportive treatments should be applied, and must be conveyed to a center for performing liver transplantation \(^{31,32}\).

**Conclusion**

The thickening of GB wall in association with acute HAV infection is a poor prognostic sign, and this indicates more conservations, more hospitalization and prolong treatment reaching to normalization.

**Conflict of interest**

None declared.

**References**


