Hepatitis A Virus Antibodies in Patients with Chronic Hepatitis B and C; A Cross-Sectional Study in Egyptian Patients.

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Abstract

Background: Acute viral hepatitis A is an inflammation of the liver with a wide range of presentations; it may result in a self-limited disease or lead to fulminant liver cell failure. It infects 1.4 million people worldwide annually. Super-infection of HAV on top of chronic viral infections, including HBV, HCV, HIV, and dengue virus, or even chronic non-viral liver disease may affect the natural course of the basic disease and lead to fulminant liver failure and higher mortality rate.

Aim of the work: To detect the seroprevalence of previous HAV infection in chronic hepatitis B and C patients in Assiut to clarify its effect on these patients and the different impacts of HAV infection on hepatitis B and hepatitis C patients.

Results: 235 patients (94 %) were HAV IgG positive, and 15 (6%) were negative. The Child-Pugh score showed more deterioration in HAV IgG-positive patients than negative patients. Of 235 HAV IgG-positive patients, 160 (68%) were HCV antibody-positive, and 75 (32%) were HBsAg positive. Patients with HAV/HCV have more impaired liver functions and lower Child-Pugh scores than HAV/HBV patients.

Conclusion: Our study showed that the prevalence of HAV infection in chronic liver disease patients is very high, as (94%) of them were positive for HAV IgG antibody. This high prevalence was associated with a significant deterioration in liver functions in chronic liver disease patients, leading to a worse prognosis. Also, we found that HAV/HCV patients showed more deteriorated liver functions than HAV/HBV patients, lower Child-Pugh scores, and worse general conditions.

Keywords: Hepatitis A virus antibody, HAV IgG, seroprevalence, chronic liver disease, hepatitis B, hepatitis C, Child-Pugh score, liver function tests

Background

Acute viral hepatitis A is an inflammation of the liver with a wide range of presentations; it may result in a self-limited disease or fulminant liver cell failure. It is a significant cause of morbidity and mortality in Egypt (1,2). Recent studies showed significant reductions in the proportions of HBV and HCV among acute viral hepatitis and an increase in HAV(3). The incidence of HAV infection is affected by socio-economic conditions, including water quality, sanitation, housing density, education, and income. (4,5)

It is endemic in Egypt; however, only a few publications provide epidemiological information based on prospectively collected sera in the general population with an adequate sample size. Specifically, more recent data from developing countries are limited. (5,6)
Unlike hepatitis B and C, HAV infection does not cause chronic liver disease. Still, infrequently, it may lead to fulminant hepatitis and more deterioration in liver functions (acute liver failure), with a reported incidence of 0.015–0.5%. Co-or superinfection of HAV with some viruses, including HBV, HCV, HEV, HIV, and dengue virus, or even in chronic non-viral liver disease, markedly affects the natural course of the basic disease and leads to the more severe outcome and liver cell failure. (7,8)

Immunoglobulins are formed once the patient gets infected by HAV. Immunoglobulin G (IgG) antibody appears simultaneously with Immunoglobulin M (IgM), but IgG dominates the antibody response, persisting for many years, if not life-long, in most individuals after infection. (4)

Total anti-HAV, including both IgM and IgG, remains positive for life after vaccination; it is useful only to identify unimmunized patients at risk. (9)

The high incidence of fulminant hepatitis in patients with combined HAV/HCV infection remains controversial; however, the Center for Disease Control and Prevention (CDC) survey demonstrated that HAV infection in patients with underlying chronic liver disease is associated with a higher mortality rate than isolated HAV infection. So, chronic liver disease is a very important risk factor in the development of fulminant hepatitis due to HAV infection in these patients with underlying liver disease such as hepatitis B and C. (10,11)

**Methods**

Our study included 250 patients with chronic liver disease due to HBV or HCV in 2017/2018. The study design was observational, a cross-sectional study that included patients diagnosed with chronic liver disease based on laboratory and ultrasonographic evidence. They underwent full history taking and clinical examination. Laboratory investigations were done to detect the Child-Pugh score: HAV IgG antibody, HBsAg, HCV Ab, AST, ALT, Bilirubin level, Albumin, and INR. Patients were divided into two main groups according to HAV IgG seropositivity: HAV IgG positive group and HAV IgG negative group, and a comparative analysis of liver function tests and Child-Pugh scores was done. Also, a comparative analysis of HBV and HCV seropositivity in the HAV IgG-positive group showed significant results.

**Inclusion Criteria:**

All patients who were attending the outpatient clinic and had chronic liver disease either due to HBV or HCV in 2017/2018. The patients’ age was between 55 – 70 years old. We defined chronic HBV as a patient with Hepatitis B surface antigen (HBsAg) positive and chronic HCV as a patient with Hepatitis C virus antibody (HCV Ab) positive.

**Exclusion Criteria:**

Patients who were previously vaccinated against hepatitis A virus and patients with hepatocellular carcinoma (HCC) were excluded from the study.

Patients with other liver diseases concomitant with HBV or HCV (Autoimmune hepatitis, Hemochromatosis, Wilson's disease, and HIV) were excluded from the study.

**Statistical Analysis**

Data were verified, coded, and analyzed using IBM-SPSS (Statistical Package for the Social Science, Version 22 and Armonk, New York, USA ). (12)

Descriptive statistics: means, standard errors, medians, and percentages were calculated. Test of significances: Chi-square and Fisher Exact tests were used to compare the difference in the distribution of frequencies among different groups. For continuous variables with more than two categories, the ANOVA test was calculated to test the mean differences of the data, and the post-hoc test was calculated using Bonferroni corrections. A
p-value equal to or less than 0.05 was considered significant.

Results

250 patients were enrolled in the study. Results showed that 235 patients (94%) were HAV IgG positive, and only 15 (6%) were negative. (Fig1)

We found the Child-Pugh scores in the HAV IgG positive group were as follows: 19 patients were Child A (8.3%), 113 patients were Child B (47.9%), and 103 patients were Child C (43.8%). Bilirubin, INR, and liver enzymes (ALT & AST) in the HAV IgG positive group were higher than the HAV IgG negative group with statistical significance. At the same time, serum Albumin was lower in the HAV IgG-positive group.

However, in the HAV IgG negative group, all patients were Child A and had much better liver function tests, representing a P-value of 0.006 and statistically significant. (Fig 2, Table1)

Comparative analysis between HBV and HCV patients who were found positive for HAV IgG antibody.

In the HBV group, 75 patients were HAV IgG positive. Child-Pugh score analysis was: 15 patients (20%) were Child A, 60 patients (80%) were Child B, and no patients found Child C in the HBV group.

However, in the HCV group, 160 patients were HAV IgG positive, we found 7 patients (4%) were Child A, 19 patients (12%) were Child B, and 134 patients (84%) were Child C with a P-value of <0.001, and that was statistically significant. (Fig 3)

Serum Albumin and liver enzymes appeared higher in the HBV group than in the HCV group. However, serum Bilirubin and INR levels were higher in the HCV group than in the HBV group, which was statistically significant with a P-value of <0.001. (Table 2)

Discussion

Egypt has a high prevalence of chronic liver disease due to chronic HCV and HBV infections. The highest HCV prevalence in the world, estimated to be 15% in some studies is in Egypt, and hepatitis B prevalence reaches (4.4%) in most studies. (13) The concomitant or superimposed infection of acute HAV leads to fulminant hepatic failure. (10,11) While the previous HAV infection has not proved to affect the progress of chronic liver disease course in our country, we conducted our study.

Serological tests showed that 31% were HBsAg positive and 69% were HCV Ab positive with no statistical significance. In Turkey, it was found that (81%) of patients tested for anti-HAV IgG were positive to HbsAg, only (11.1%) were HCV Ab positive, and (7.9%) were cirrhotic patients; the reverse occurred in Italy, where about (75%) of tested patients were HCV Ab positive, (25%) were HBsAg positive, and both studies did not show any significance. (14,15)

All patients in our study were tested for HAV IgG antibody. Results showed that 235 patients (94%) were positive for anti-HAV IgG and 15 patients (6%) were negative, with near incidence to study conducted in Saudi Arabia, anti-HAV IgG seropositivity was 134 patients (98.5%) out of a total 136 chronic liver disease patients tested. (16)

In the Kerala region of India, anti-HAV IgG seropositivity was (93.3%) in chronic liver disease patients. (17) In Brazil, it was (98.1%). (18) In Iran, it was (79.2%) in patients with chronic viral hepatitis, and hepatitis A vaccination was subsequently recommended for all patients with chronic viral hepatitis who were younger than 30 years old. (19) Also, in Korea, in one of the two recent studies, the anti-HAV IgG seropositivity was (86.61%) in chronic hepatitis patients. In another study where only patients with chronic hepatitis B were assessed, the anti-HAV IgG seropositivity was found to be (49.1%). (20,21)
Compared with two developed countries, in the USA, anti-HAV IgG seropositivity was (55%) in patients with chronic liver disease. (22) However, in Italy, they found (53.5%) were positive for total anti-HAV antibodies. (23)

We concluded from these studies that HAV seroprevalence in chronic liver disease patients is very high, especially in developing countries, so improving socioeconomic status, more sanitary environments, and advanced hygienic practices, all play a role in reducing the incidence of HAV infection in the general population reducing subsequent morbidity and mortality.

Analysis of liver functions in the HAV IgG positive group showed more deteriorated liver functions, lower Child-Pugh scores, and worse general condition than the negative group. This clearly showed the effect of previous HAV infection on chronic liver disease course as the mean Child-Pugh score in most HAV IgG positive patients is between Child B and C. However, all patients (100%) negative to HAV IgG antibody were Child A.

Other studies confirmed this result as they showed that HAV concomitant infection in chronic liver disease patients led to more laboratory abnormalities and more severe disease, including fulminant hepatic failure and a higher case fatality rate. (24)

In Thailand, they found that no one of 100 patients with isolated acute HAV infection developed severe hepatitis. However, in HBsAg carriers and chronic liver disease patients due to either HBV or HCV, they found (55%) of the HBsAg carriers and (33%) of total chronic liver disease patients developed fulminant or submassive hepatitis with high mortality rates reached about (25%) and (33%) respectively. (25)

Also, a study done in Turkey confirmed that hepatitis A is a self-limiting disease generally, but it may lead to more severe disease and worse outcomes if it is concomitant with chronic hepatitis B. (26,27)

Analysis based on HBV or HCV serological tests revealed that HAV/HCV patients were more affected. They had more deteriorated liver functions and lower Child-Pugh scores than HAV/HBV patients. The most dramatic observation of this result was seen in a well-cited Italian study where most HAV/HCV patients developed acute or fulminant hepatitis with a high mortality rate; however, HAV/HBV patients showed a much better prognosis, and this matches our results. (28,29)

Our current study needs to be performed on more patients and in multiple centers all over Egypt. Further research is required to clarify worse prognosis in HAV/HCV patients than in HAV/HBV patients.

Conclusions

Sero-prevalence of HAV infection in our society is very high, similar to other developing countries, and this could be minimized by enhancing socio-economic levels, advanced hygienic practices, and education.

Old or previous HAV infection in patients with chronic hepatitis B and C greatly affects disease progress. It carries a higher risk and worse prognosis, so we highly recommend close observation and follow-up of this high-risk group as well as empiric vaccination against HAV for all patients who were newly diagnosed to be HBV or HCV positive.

Our study revealed that previous HAV infection is much more serious in HCV patients and carries a worse prognosis than in HBV patients. However, more studies are needed on a larger number of patients.
List of Abbreviations

<table>
<thead>
<tr>
<th>Ab</th>
<th>Antibody</th>
<th>HBsAg</th>
<th>Hepatitis B surface antigen</th>
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<tr>
<td>ALB</td>
<td>Albumin</td>
<td>HBV</td>
<td>Hepatitis B virus</td>
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<tr>
<td>ALT</td>
<td>Alanine transferase</td>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transferase</td>
<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
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<tr>
<td>Bil</td>
<td>Bilirubin</td>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>CLD</td>
<td>Chronic Liver Disease</td>
<td>IgM</td>
<td>Immunoglobulin M</td>
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<tr>
<td>HAV</td>
<td>Hepatitis A virus</td>
<td>INR</td>
<td>International Normalized Ratio</td>
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Figure Legends

Fig. 1: Classification of patients according to HAV IgG seropositivity.
Fig. 2: Child-Pugh score classification categories according to HAV IgG seropositivity.

Fig. 3: Distribution of Child-Pugh score classification categories of HBV and HCV patients.

**Tables**

**Table 1: Comparative analysis according to HAV IgG seropositivity.**

<table>
<thead>
<tr>
<th></th>
<th>HAV IgG Negative (No.=15)</th>
<th>HAV IgG Positive (No.=235)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Albumin</td>
<td>36.50 ± 0.7</td>
<td>28.50 ± 3.5</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>32.50 ± 0.7</td>
<td>43.08 ± 7.7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>INR</td>
<td>1.55 ± 0.1</td>
<td>2.02 ± 0.2</td>
<td>0.020*</td>
</tr>
<tr>
<td>AST</td>
<td>55.00 ± 1.4</td>
<td>69.75 ± 4.9</td>
<td>0.006*</td>
</tr>
<tr>
<td>ALT</td>
<td>53.00 ± 4.2</td>
<td>63.65 ± 4.1</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

*An independent t-test was used to compare the mean difference between groups.
**The Fisher Exact test was used to compare the proportion differences.
Table 2: Comparative analysis in HAV positive group between HBV and HCV patients.

<table>
<thead>
<tr>
<th></th>
<th>HBV (No.=75)</th>
<th>HCV (No.=160)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>31.68 ± 2.4</td>
<td>25.96 ± 2.4</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>36.72 ± 5.9</td>
<td>48.60 ± 4.2</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>INR</td>
<td>1.82 ± 0.1</td>
<td>2.18 ± 0.2</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>AST</td>
<td>84.76 ± 7.8</td>
<td>53.56 ± 3.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>ALT</td>
<td>75.76 ± 6.5</td>
<td>50.68 ± 3.1</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*The Chi-square test was used to compare the proportion differences.
References


16. Singal AK. Hepatitis A vaccine is not required in adult patients with chronic liver disease in Saudi Arabia.


