Prevalence of H. Pylori Infection in Non-Cirrhotic Patients with Chronic Delta Hepatitis

Hasan Mücahit Özbaş¹, Ahmet Cumhur Dülger², Elif Tugba Tuncel³
İskender Aksoy⁴, Mustafa Yakanşık⁵, Merih Şimşek⁶, Mesut Aydın⁷*

1 Giresun University School of Medicine, Division of Hematology, Giresun, TR
2 Giresun University School of Medicine, Division of Gastroenterology, Giresun, TR
3 Manisa Public Hospital, Division of Gastroenterology, Manisa, TR
4 Giresun Public Hospital, Division of Emergency Medicine, Giresun, TR
5 Giresun University School of Medicine, Division of Internal Medicine, Giresun, TR
6 Afyonkarahisar Health Sciences University School of Medicine, Division of Microbiology, Afyonkarahisar, TR
7 Van Yuzuncu Yıl University School of Medicine, Division of Gastroenterology, Van, TR

* Corresponding Author: Mesut Aydın E-mail: gmstaydin@gmail.com

ABSTRACT

Objective: The relationship between Hepatitis Delta infection and Helicobacter infection in patients with non-cirrhotic hepatitis B infection was retrospectively investigated.

Material and Methods: Stool samples of 117 patients included with Delta hepatitis infection in the study At total 36 of them were tested for H. Pylori infection. To detect H. Pylori, stool samples were tested using a commercial stool H. Pylori antigen assay.

Results: Of these, 13 (19%) patients had H. Pylori seropositivity in the Hepatitis B infection group and 23 (48%) patients tested positive for H. Pylori infection in hepatitis delta infection group. There was a statistically significant difference between groups regarding H. Pylori seropositivity by the faecal test (p= 0.001).

Conclusion: This study provides new knowledge on H. Pylori infection and reflects the need for evidence-based and comorbid diseases-oriented guidelines in the field of gastroenterology.

Keywords: Hepatitis B, Delta Hepatitis, Helicobacter pylori

INTRODUCTION

Hepatitis delta virus (HDV) infection is generally rare among hepatitis B virus-infected patients and contributes to more severe disease, including advanced cirrhosis and hepatocellular carcinoma compared to hepatitis B infected patients (1). HDV, which does not have the ability to cause infectious disease on its own, can only perform replication and transmission in the presence of the Hepatitis B virus (HBV). In other words, HDV causes hepatitis in humans in the presence of HBV. HDV genome, a single-stranded RNA virus, is not homologous to the HBV genome and is not organized like hepadnavirus. The HDV genome is surrounded by an envelope and core containing HBsAg. The delta antigen (core), which contains the HDV genome, attaches to hepatocytes via HBsAg, enters the cell and performs replication (2). Helicobacter pylori is a gram-negative bacterium that can cause peptic ulcers, gastritis and stomach cancer. Thus, it has a higher prevalence in less developed countries as it constitutes 50% of the infected population. However, H. Pylori infection is one of the most common causes of gastric cancer and is classified as a major human carcinogen (3). It has been reported that overcrowded populations, lack of infrastructure, poor hygienic conditions and lower socioeconomic status are associated with higher prevalence of H. Pylori infection (4).

Apart from these, it has been reported that premalignant gastric lesions associated with H. Pylori, including chronic inactive gastritis, atrophy and intestinal metaplasia, are common, especially among Eastern Asians who are at high risk for HDV infection.

Demographic and socioeconomic conditions have been reported to be highly influential on H. Pylori gastritis and its pre-neoplastic lesions in individuals in the USA (5). So we mainly focused on the connection between H. Pylori infection and HDV infection as both infections remain high in the eastern region of Turkey, where the similar epidemiologic factors could be a key for spreading both infections.
MATERIAL and METHODS

The relationship between Hepatitis Delta infection and Helicobacter infection in patients with non-cirrhotic hepatitis B infection between January 2020 and April 2021 at Yüzüncü Yıl University Faculty of Medicine in Turkey, close to the Turkish-Iranian border, was retrospectively investigated. Stool samples of 117 patients were included in the study. At total 36 of them were tested for H. Pylori infection.

Those with gastric or hepatic surgery, hepatocellular or gastric carcinoma, H. Pylori treatment at least three weeks prior to study enrolling, missing values for analyses, or cirrhosis were excluded. Patients with ultrasonographically-proven splenomegaly and liver cirrhosis were not included. We also excluded those with proton pump use in the preceding three months.

To detect H. Pylori, stool samples were tested using a commercial stool H. Pylori antigen assay kit with 95% specificity (GI Supply, Camp Hill, PA, USA).

HBV-DNA was determined with the Artus HBV-DNA-QS-RGQ kit (Qiagen, Germany). HDV-RNA was determined using the single-step primer RT-PCR kit (Primer design, UK) and Rotor Gene Q Real time PCR (Qiagen, Germany). Anti-HDV, IgG anti-HBe and HBsAg levels were determined by ELISA (Cobas 601, Roche, Germany).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 program. Descriptive statistics for continuous variables were evaluated as mean deviation, median, minimum and maximum values, standard deviation, and categorical data as numbers and percentages. The Kruskal-Wallis test was used for continuous variables in the comparison of the groups. The χ2 test was used to evaluate the significance of the difference between the ratios of the analysis. P value < 0.05 was accepted as significant.

RESULTS

There were 69 patients (The mean age was 51.4 years and 28 (42%) of them were female) with chronic hepatitis B without chronic hepatitis delta infection and were 48 patients (The mean age was 53.7 years and 21 (43.8%) of them were female) those tested positive for hepatitis delta virus. There were no gender and age gap between groups ( p = 0.85 and p = 0.06, respectively).

Of these, 13 (19%) patients had H. Pylori seropositivity in hepatitis B infection group and 23 (48%) patients tested positive for H. Pylori infection in hepatitis delta infection group. There was a statistically significant difference between groups in terms of H. Pylori seropositivity by fecal test (p = 0.001). At both of virologic and serologic perspectives, the rate of Hbe antigen positivity and serum HBV DNA levels were similar between groups [(5 patients tested positive for hepatitis e antigen in hepatitis B group and 3 patients tested positive in hepatitis D group ( p = 0.9) and 3173 copy per cubic milliliter in hepatitis B group versus 3663 copy per cubic milliliter in hepatitis delta group ( p = 0.209)]. While the mean HDV RNA level was 14641 copies per cubic milliliter in patients with chronic hepatitis delta patients, no patients had any positive HDV RNA result among those hepatitis B group.

By the multivariate logistic regression, the patients with chronic delta hepatitis had higher transaminases AST and ALT levels compared to those without. (74 u/L. versus 26 u/L. p = 0.001 and 106 u/L. versus 35 u/L. p = 0.001; respectively.) Furthermore, the mean platelet levels were significantly lower in the hepatitis delta group compared to the hepatitis B group despite the lack of any cirrhotic patient in the study population. 171,000 per cubic milliliter versus 256 per cubic milliliter (p = 0.001). No significant differences of the remaining biochemical and hematologic biomarkers were detected between groups ( p > 0.05). Baseline characteristics of the patients were depicted in the Table 1.

Table 1: Baseline characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Anti HDV -</th>
<th>Anti HDV +</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP antigen in stool</td>
<td>HP -</td>
<td>55 (80.9)</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td></td>
<td>HP +</td>
<td>13 (19.1)</td>
<td>23 (47.9)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>40 (58)</td>
<td>27 (56.5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>29 (42)</td>
<td>21 (43.8)</td>
</tr>
</tbody>
</table>
Hepatitis delta virus (HDV) is a small, defective RNA virus that infects individuals globally. Again, the prevalence of HDV infection is associated with HDV persistence. This is the first study in the Mediterranean countries as well as in eastern part of Turkey. Where the prevalence of HDV reaches close to 25% (6,7).

Co-infection with HDV and HBV is the most severe form of viral hepatitis. Super-infection of these two viruses is highly likely to develop into chronic hepatitis. Chronic delta hepatitis is the most severe form of chronic viral hepatitis and is the most rapidly progressive form of the disease. High-dose and long-term interferon therapy is the only option for this type of hepatitis with a high need for treatment. Recovery from HDV and HBV co-infection usually occurs when both viruses are cleared from the blood. Chronic HBV-HDV super-infection is associated with HDV persistence. This situation increases the risk of Cirrhosis and Hepatocellular Carcinoma (2,8). When we look at the world data, various estimations regarding the prevalence rates of HBV and HDV, remark. Approximately 468 million people are estimated to be infected with HBV, according to a meta-analysis conducted in 2018. It is also estimated that about 49.5 million of these people infected with HBV are co-infected with HDV (9). Although HBV positivity is naturally determined at higher rates than HDV positivity in the society, there are increasing opinions that HDV positivity may be higher than the determined rates (10,11). According to a meta-analysis study data by Stockdale et al. in 2020, the global prevalence of anti-HDV in the general population is suspected to be 4.5% among HBsAg-positive individuals, compared to 6.0% in Africa and 3.0% in Europe. This rate represents an estimated 12 million HDV seropositive individuals globally. Again, according to the aforementioned study data, Mongolia has the highest national prevalence of anti-HDV (36.9%), while this rate is reported to be over 10% for Moldova and countries in West and Central Africa (2).

DISCUSSION

This is the first study in the literature examining the seroprevalence of H. Pylori infection in patients with non-cirrhotic chronic HDV infection. The seroprevalence of chronic HDV infection is as high as 15% in a Mediterranean basis. In addition, it is mainly seen in the eastern and southeastern part of Turkey, where the prevalence of HDV reaches close to 25% (6,7).

According to an analysis study by Shen et al. in 2019, the world overall seroprevalence of HDV was estimated to be 1.06% in 2017–2018, while the rate was 7.66% in the mixed population. It has been reported that the world general seroprevalence of HDV was 1.00% between 1977 and 2018, and the global burden of HDV infection corresponded to approximately 74 million people. When comparing countries’ HDV prevalences, China shares the largest rate, with Pakistan in second place (8). In a study conducted by Karlıdağ in 2019, anti-HDV-seropositivity in Turkey was determined at the rate of 8.8% (12). The prevalence of HDV was determined to be 2.8% in Turkey in 2021 by Bal et al. Thus, the delta hepatitis infection curve is rising in the middle east than those western worlds largely due to socioeconomic turmoils in recent decades (13). Today, hepatitis delta virus (HDV) infection continues as a health problem in some parts of the world and the eastern part of Turkey.

Otherhand, the prevalence of H. Pylori infection is also higher in Mediterranean countries as well as in the eastern part of Turkey and is reported in a prevalence with up to 65% due to low socioeconomic status, lack of health care and due to political turmoil (14).

Thus, the burden of described diseases is even higher for subjects who lived in the Middle East as well as in eastern Turkey, where the current study was conducted (Table 2).

Hepatitis delta virus (HDV) is a small, defective RNA virus and causes a wide range of liver diseases, including cirrhosis and hepatocellular carcinoma, then those patients with naïve hepatitis B infection (15).

In a historical study conducted in an HDV prevalent African country, lower economic status, decreased number of rooms per household, increased number of persons per household, lack of water supply, low money income per capita and low health conditions were all associated with the increased rate of HDV infection (16).

<table>
<thead>
<tr>
<th>n</th>
<th>Anti HDV - Mean (95% CI)</th>
<th>Anti HDV + Mean (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67</td>
<td>47.4 (44.1 - 50.7)</td>
<td>48</td>
</tr>
<tr>
<td>Hbe Ag</td>
<td>67</td>
<td>0.365 (0.062 - 0.675)</td>
<td>48</td>
</tr>
<tr>
<td>Anti-Hbe</td>
<td>69</td>
<td>0.817 (0.554 - 1.079)</td>
<td>48</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>42</td>
<td>3173 (1058 - 5289)</td>
<td>48</td>
</tr>
<tr>
<td>HBV RNA</td>
<td>69</td>
<td>14641 (2737 - 26545)</td>
<td>48</td>
</tr>
<tr>
<td>WBC</td>
<td>68</td>
<td>6.6 (6.29 - 7.46)</td>
<td>48</td>
</tr>
<tr>
<td>RBC</td>
<td>69</td>
<td>5.01 (4.77 - 5.24)</td>
<td>48</td>
</tr>
<tr>
<td>Hbg</td>
<td>68</td>
<td>14.49 (13.88 - 15.09)</td>
<td>47</td>
</tr>
<tr>
<td>Htc</td>
<td>68</td>
<td>44 (42.2 - 45.8)</td>
<td>48</td>
</tr>
<tr>
<td>MCV</td>
<td>68</td>
<td>86.6 (85.0 - 88.2)</td>
<td>48</td>
</tr>
<tr>
<td>PLT</td>
<td>68</td>
<td>256 (239 - 272)</td>
<td>48</td>
</tr>
<tr>
<td>Iron</td>
<td>49</td>
<td>85.94 (71.38 - 100.51)</td>
<td>38</td>
</tr>
<tr>
<td>TIBC</td>
<td>48</td>
<td>230 (204 - 255)</td>
<td>38</td>
</tr>
<tr>
<td>Ferritin</td>
<td>56</td>
<td>140.82 (96.15 - 185.49)</td>
<td>37</td>
</tr>
<tr>
<td>Folat</td>
<td>45</td>
<td>7.4 (6.4 - 8.4)</td>
<td>32</td>
</tr>
<tr>
<td>B12</td>
<td>51</td>
<td>346 (294 - 398)</td>
<td>32</td>
</tr>
<tr>
<td>AFP</td>
<td>46</td>
<td>4.03 (1.99 - 6.06)</td>
<td>46</td>
</tr>
<tr>
<td>Glucose</td>
<td>63</td>
<td>104 (94 - 114)</td>
<td>47</td>
</tr>
<tr>
<td>AST</td>
<td>69</td>
<td>26 (18 - 34)</td>
<td>48</td>
</tr>
<tr>
<td>ALT</td>
<td>67</td>
<td>35 (19 - 50)</td>
<td>48</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>66</td>
<td>0.84 (0.58 - 1.10)</td>
<td>47</td>
</tr>
<tr>
<td>BUN</td>
<td>56</td>
<td>15.42 (13.53 - 17.31)</td>
<td>46</td>
</tr>
<tr>
<td>Creatinin</td>
<td>67</td>
<td>0.88 (0.77 - 0.99)</td>
<td>48</td>
</tr>
</tbody>
</table>
In a recent study from eastern Turkey showed that living in rural areas and being female gender were linked to having HDV infection than those without (17).

Furthermore, overcrowded families could be responsible for further spreading HDV infection as well(18).

From the same epidemiologic perspective, H. Pylori infection is also associated with poor hygiene and sanitation, low familial socioeconomic status and unsanitized water sources similar to HDV-related epidemiologic factors (19).

We postulated that poverty and socioeconomic turmoil increases the risk of having H. pylori, as does HDV infection. It has also been reported that gastric biopsy-proven H. Pylori infection was also associated with HDV infection compared to HBV-related cirrhotic patients. But the study patients had mostly advanced liver cirrhosis, and its sample size was very diminished (20).

It has been reported that, patients with chronic HDV infection had more ACA positivity compared to patients with HBV infection (21).

Furthermore, HDV infection perturbs the hepatocytes functions as does the thyroid diseases (22).

**CONCLUSION**

We concluded that these HDV-related down-regulations of the immune system could result in gastric mucosal damage and can increase the rate of H. Pylori infection among the vast majority of patients with chronic HDV infection. If synergism between H. Pylori infection and hepatitis delta infection should be kept in mind, all patients with chronic delta hepatitis should also be screened for H. Pylori infection, thus preventing peptic ulcer and gastric carcinoma could be obtained in large populations who faced chronic delta hepatitis infection. This study provides new knowledge on H. Pylori infection and reflects the need for evidence-based and comorbid diseases-oriented guidelines in the field of gastroenterology.

**Limitations:** The most critical limitation of this study is a retrospective study, so the risk factors could not be determined. This study limits accuracy for interregional comparison, as the data are from a single centre. What is unclear is whether the prevalence of HP will continue to change or remain stable. HP prevalence is generally higher in developing countries, but recent reports are not available for many developing countries. At this point, it was difficult to make healthy comparisons with our data. Despite these limitations, this study provides an overview of the current state of HP. These data may guide further studies to prevent HP by reducing complications of HP and to support regional interventions.

**Acknowledgement:** None

**Author Contributions:** HMÖ, ACD, ETT, İA, MY, MŞ, MA: Concept, Data collection and/or processing, Analysis and/or interpretation, Literature review, MA: Writing, Revisions.

**Conflict of interest:** The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

**REFERENCES**


