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Does Helicobacter pylori infection play a role in susceptibility to Brucellosis?

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Running Title: Helicobacter pylori and Brucellosis

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**Keywords:** Brucellosis, Helicobacter pylori, Kurdistan
SUMMARY: Brucellosis is endemic in Iran. Several studies show that brucellosis is associated with other infectious diseases. This study aimed to determine the relationship between brucellosis and Helicobacter pylori. In this case-control study, 100 patients with brucellosis as cases and 200 participants without brucellosis as controls were evaluated. To compare the prevalence of Helicobacter pylori in the two groups, odds ratio and confidence intervals for every variable were analyzed through using logistic regression model after adjustment for confounding factors. The results obtained in patients with brucellosis showed that fever, sweating and joint pain were the most prevalent clinical symptoms among the studied patients; in addition, compared with the control group, there was a significant relationship between the IgM antibody to Helicobacter pylori and brucellosis infection (P=0.001). Taking into account a 95% confidence interval, the estimated odds ratio was 2.74 (CI_{95%}: 1.5 – 4.9). Acute infection with Helicobacter pylori was associated with brucellosis and increased the risk of brucellosis infection.

Brucellosis is the most common zoonotic disease in the world(1). Iran is among hyper endemic regions in the world; Kurdistan province is among the provinces with high incidence of the disease (2,3). Brucella bacteria often attacks reticuloendothelial system and can remain in infected macrophages in different parts of the body. Tcell CD4 + Tcell
CD8$^+$ make protection against the disease; moreover, TH1 is effective in deterioration of the disease. In addition, interleukin 12 can cause the disease presentation via stimulating IFN gamma and generating TH1 responses (4).

Recently, many studies have been conducted on the relationship between Helicobacter pylori (HP) infection and other infectious and noninfectious diseases (4,5). Several studies have investigated the link between this disease and blood groups, chronic hepatitis C, IgA nephropathy (4,6-9). Furthermore, the protective role of HP against tuberculosis and shigellosis and other diarrheal diseases are also studied (10-11).

Because interferon-gamma is one of the important factors controlling the infection with intracellular microbial pathogens, it is hypothesized that HP infection may also alter the resistance to brucellosis. Also, we can hypothesize that given that HP infection is also transmitted orally, the presence of HP together with reducing stomach acid can increase the risk of brucellosis infection. So this study aimed to determine the relationship between these two diseases.

This case-control study was approved by ethic committee in Kurdistan University of Medical Sciences (ethic code: MUK.REC.1391.144). Considering a power of 80%, Type I error of 5%, a 40% prevalence of HP in the control group, odd ratio of 2, a case-to-control ratio of to 1 to 2, and using Kelsey formula, sample size was calculated as 100 for
cases and 200 for controls. The brucellosis patients were tested and diagnosed in Tohid hospital (Sannandaj, Iran). Exclusion criteria for both patients and the control group were the followings: history of gastritis and peptic ulcer, history of using an antibiotic in the past few months, history of using proton pump inhibitors and H2 blocker in the past month, history of using any type of anti-acid drug or undergoing stomach and intestines surgery.

When the result of Wright test was 1/160 and when the result of Coombs Wright test was 1/80, the case was positive (12). The control group was selected from among people who referred to the laboratory ward of the same hospital to perform routine tests. Exclusion criteria for this group were similar to patients group, plus history of brucellosis and positive Coombs Wright test. Control group were matched by group matching according to gender, location, and age (±5 years). HP was detected based on the rate of H-pylori antibodies tested via ELISA method; accordingly, IgG and IgM levels were measured.

To compare the prevalence of HP in the two groups, we used chi-square or Fisher tests and we calculated Odds Ratio (OR) and its confidence intervals using SPSS 17 software. Then for controlling the effects of confounding factors, we used logistic regression method.

The mean age of the patients was 37.7±16.8 years and the mean age of the control group
was 39.9±17.9 years (p=0.558). Of all cases, 73 persons (73%) were male and 85 persons (85%) were rural. According to the results of univariate analysis (Table 1), IgG HP antibody was positive in 55 patients (55%) in the case group and 108 (54%) in the control group (p=0.48), but IgM antibody to HP was positive in 30 patients (30%) in the case group and 27(13%) in the control group. In addition, the prevalence of positive IgM antibody to HP in the case group was 2.74 times more than that in the control group (p=0.001).

In multivariate analysis, we found that there was a significant relationship between brucellosis and positive IgM antibody to HP (p=0.001) and there was a higher prevalence of IgM antibody to HP among the people infected with brucellosis (Table 2).

In our study, positive IgG antibody to HP was observed in 55% of cases and 54% of the controls, however positive IgM antibody to HP was observed in 30% and 13% of cases and controls, respectively. Esen et al. (12) reported that the prevalence of positive IgG to HP was 69% in patients with brucellosis and 87% in healthy subjects; their results are almost consistent with our results, however IgM level is not assessed in their study of. A limitation of the Esen et al.’s study (13) was the lack of matching between groups in terms of age, sex, and location; these items can act as confounding factors. Our study did not face this limitation. In our study, acute infection with HP was associated with brucellosis
infection. There is raised IgG in the active HP and IgM may remain high for long time after curing the disease.

Vollaard et al.’s study (14) showed that chronic infection with HP may affect and decrease gastric acid secretion and lead to peoples susceptibility to Salmonella typhi infection. Reduced gastric acidity due to chronic infection with HP was a risk factor for typhoid fever. However, given the fact that in our study, IgM antibody to HP was associated with Malta fever, and since in acute Helicobacter infection there is no significant reduction in gastric acid and atrophic gastritis, it seems that some mechanisms other than the above mentioned mechanisms are involved in the development of Malta fever in patients with HP infection.

In another study, the rate of infection with HP in patients with tuberculosis was more than that in normal subjects. Given that the method of transmission of these diseases is different, genetic factor is assumed as a risk factor. Studies show that the HLA-DQ serotypes is associated with increased survival and proliferation of Mycobacterium and this HLA exists in people susceptible to brucellosis (15). During HP infection, neutrophils and B and T cell infiltration occurs in the mucosa of the stomach and duodenum but it cannot clear the infection, which is probably due to the lack of cytokines and down regulation of immune response which is caused by T regulatory cells. Innate and adaptive
immune responses to HP infection generates inflammatory responses and can lead to survival of infections (16). Other studies also have shown that during infection with Helicobacter, the number of T regulatory lymphocytes cells increases and the rate of cytokine production decreases (17-19). Increased activity of T regulatory lymphocytes is associated with the stability of infections such as leishmaniasis, malaria, and tuberculosis; it suggests the possible association between the survival and persistence of pathogens and immune suppression by T regulatory cells (20). However, one study showed that T regulatory lymphocytes did not increase in peripheral blood in patients with HP infection, and it activates humoral immune system and TH2 polarization and these changes lead to an autoimmune system disorder (21).

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Conflicts of interest: No

References:


Table 1. Comparison of variables between cases and controls

<table>
<thead>
<tr>
<th>Helicobacter pylori antibody</th>
<th>Frequency (%)</th>
<th>OR (95% Confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case (n=100)</td>
<td>Control (n=200)</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>55 (55)</td>
<td>108 (54)</td>
<td>1.04 (0.6 – 1.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>45 (45)</td>
<td>92 (46)</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>30 (30)</td>
<td>27 (13)</td>
<td>2.74 (1.5 – 4.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>70 (70)</td>
<td>173 (87)</td>
<td></td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>67 (67)</td>
<td>120 (60)</td>
<td>1.35 (0.8 – 2.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>33 (33)</td>
<td>80 (40)</td>
<td></td>
</tr>
</tbody>
</table>

OR: Odds Ratio

Chi-square test was used for analysis.
Table 2. Results of logistic regression analysis to examine the association between Helicobacter pylori infection and brucellosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta</th>
<th>Standard Error</th>
<th>P-value</th>
<th>Adjusted OR</th>
<th>OR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>0.127</td>
<td>0.286</td>
<td>0.657</td>
<td>1.136</td>
<td>0.648</td>
<td>1.989</td>
<td></td>
</tr>
<tr>
<td>Residency (Urban/Rural)</td>
<td>-0.138</td>
<td>0.351</td>
<td>0.695</td>
<td>0.871</td>
<td>0.438</td>
<td>1.735</td>
<td></td>
</tr>
<tr>
<td>IgG positive (H.Pylori)</td>
<td>0.013</td>
<td>0.252</td>
<td>0.958</td>
<td>1.013</td>
<td>0.618</td>
<td>1.662</td>
<td></td>
</tr>
<tr>
<td>IgM positive (H.Pylori)</td>
<td>1.043</td>
<td>0.307</td>
<td>0.001</td>
<td>2.837</td>
<td>1.555</td>
<td>5.174</td>
<td></td>
</tr>
</tbody>
</table>

OR: Odds Ratio

H.Pylori: Helicobacter pylori