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SHORT COMMUNICATION

Helicobacter pylori infection is not correlated with subclinical thrombocytopenia: A cross-sectional study

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Abstract

In a small percentage of patients with immune thrombocytopenia (ITP), *H. pylori* eradication has a positive effect on platelet counts. Whether *H. pylori* infection is associated with a lower thrombocyte count in persons without clinical ITP is unknown. We performed a cross-sectional study to compare thrombocyte count between *H. pylori* infected ($n = 108$) and *H. pylori* non-infected patients ($n = 600$) who underwent a diagnostic gastroscopy. The mean thrombocyte count in *H. pylori* negative patients was 257×10^9/l, in *H. pylori* positive patients 252×10^9/l (mean difference 5×10^9/l, 95% CI: −23 to 14). Subgroup analysis did not show significant differences either. In the patient group without apparent comorbidity, there were no subjects with thrombocyte counts <120. In 36 *H. pylori* positive patients in whom data post-eradication was available, platelet counts pre- and post-eradication were similar. In conclusion, this study could not demonstrate a lower thrombocyte count in *H. pylori* infected patients or in subgroups of *H. pylori* infected patients compared to non-infected subjects.

Keywords

Helicobacter pylori, trombocytopenia

History

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Introduction

In a small percentage of immune thrombocytopenia (ITP) patients infected with *H. pylori*, eradication of the bacteria has a positive effect on platelet counts [1, 2]. The pathogenesis of this phenomenon is not entirely clear. Hypothesized pathophysiological mechanisms for thrombocytopenia related to *H. pylori* infection are mainly immunological, such as stimulation of autoreactive B-cell clones, and cross-mimicry between epitopes of glycoproteins on thrombocytes and antigens against *H. pylori* [3]. Host-mediated factors such as human leukocyte antigen patterns have also been mentioned [4]. Despite an adequate inflammatory response, *H. pylori* infection usually persists for life without antibiotic intervention [5]. If an effect of *H. pylori* on thrombocytes exist, the low grade inflammatory response that remains present during life [6], might lead to a lower thrombocyte count even in the absence of ITP.

H. pylori infection is highly prevalent; in developing countries, nearly everyone is infected by the age of 50 years. [5] Prevalence in developed countries is decreasing rapidly due to effective treatment. ITP on the other hand has an annual incidence of ∼11/1 000 000 [7]. Thus, although *H. pylori* infection is not a sufficient cause for thrombocytopenia, among *H. pylori* infected persons subgroups may be identifiable in whom thrombocytopenia occurs. The identification of these groups would aid in the understanding of the pathophysiological route to thrombocytopenia in *H. pylori* infected patients.

We compared thrombocyte counts between *H. pylori* infected and *H. pylori* non-infected patients who underwent a diagnostic gastroscopy. We hypothesized that a lower thrombocyte count might be found in *H. pylori* infected patients or in subgroups of *H. pylori* infected patients compared to non-infected subjects.

Design and methods

Study design

We performed a cross-sectional study to compare thrombocyte count between *H. pylori* infected and *H. pylori* non-infected patients. Charts of all patients who underwent a diagnostic gastroscopy from 1 January 2010 to 31 December 2011 in the Leiden University Medical Center, a tertiary teaching hospital, were reviewed for *H. pylori* status: thrombocyte count, white blood cell count and hemoglobin.

Patients

All patients in whom a biopsy and cultures for *H. pylori* were taken were included in the study, regardless of disease type or indication for gastroscopy. Patients were defined *H. pylori* positive when either the light microscopy or the tissue cultures proved to be positive.

We abstracted the presence of underlying diseases with known effect on thrombocyte count (malignancies, alcohol abuse, autoimmune diseases, hepatitis B, hepatitis C, HIV, liver cirrhosis and liver transplant patients) and diseases without known effect on thrombocyte count (iron deficiency/anemia, upper abdominal complaints, miscellaneous) based on a review of charts from patients included for study. This miscellaneous group is

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heterogeneous and consisted of patients who underwent gastroscopy for screening for malignancy, people with venous thrombosis and unexplained weight loss as well as constipation and screening for suspected celiac sprue.

Laboratory analysis

All cell counts (thrombocytes, leucocytes and hemoglobin) were performed for routine medical practice purposes with an automated cell counter (XE-2100, Sysmex, Sysmex Corporation, Kobe, Japan). For all patients, the thrombocyte count closest to the gastroscopy was extracted, preferably at day of the procedure. Since *H. pylori* is a chronic infection, blood cell counts were taken into account up to 1 year before gastroscopy, assuming that the infection was contracted well before gastroscopy and thus a possible effect would have started earlier.

If available, for infected patients, thrombocyte count post-eradication was noted. We used the first thrombocyte count available at least 3 weeks but no longer than 1 year after eradication therapy. The time limit of 3 weeks was chosen because response time after therapy is estimated 2 weeks [8], plus one week for completing the 7-day regimen.

Diagnostic procedures

In all patients, gastroscopy was performed for various clinical indications. No patients underwent gastroscopy for study reasons. Standard procedures included two biopsies for pathology analysis and one biopsy for tissue culturing from the antrum, as well as a similar procedure in the corpus, using a standard gastric biopsy forceps (Radial Jaw, Boston Scientific, Natlick, USA). Light microscopy was used to confirm presence of *H. pylori*. In case of doubt, additional immunohistochemical dyeing was performed. Biopsies were cultured for *H. pylori*.

Statistical analysis

Differences in platelet count, hemoglobin and white blood cell count between *H. pylori* infected and non-infected subjects were tested in a linear regression model. Sub-analyses were performed stratified by underlying disease categories as described earlier. Differences in platelet count pre- and post-eradication were analyzed using a paired *t*-test. Analyses were adjusted for age and sex. p value <0.05 was considered statistically significant. Analyses were performed using STATA Statistical Software (StataCorp 2011, Release 12; College Station, TX: StataCorp LP).

Results and discussion

In total, 899 patients underwent a diagnostic gastroscopy with biopsies for *H. pylori* examination between 2010 and 2011. Of these patients, 191 could not be included because thrombocyte counts were not routinely measured. Details of 708 included patients are shown in Table I. The mean age was 53 years, 55% were women. Patients with upper abdominal complaints comprised the largest group (45%). Of the included patients, 600 were *H. pylori* negative and 108 *H. pylori* positive. Men were more often *H. pylori* positive than women (19 vs. 12%, respectively). In total, 20 patients in the *H. pylori* negative group had platelet counts under 100×10^9/l, with a mean platelet count of 77×10^9/l (95% CI: 67–87). Of all *H. pylori* infected patients, three had platelet counts under 100×10^9/1 with a mean platelet count of $61 \times 10\ 10^9$/l (95% CI: 13–109).

The mean thrombocyte count in *H. pylori* negative patients was 257×10^9/l, in *H. pylori* infected patients the mean thrombocyte count was $252 \times 10\ 10^9$/l, mean difference 5×10^9/l, (95% CI: −23 to 14). Mean platelet counts in *H. pylori* positive patients were thus not different from mean platelet counts in *H. pylori* negative patients. Stratified by underlying disease/indication for gastroscopy, also no clearly lower thrombocyte count could be shown in *H. pylori* positive patients (Table II).

Table I. Patient characteristics.

	Total *n* (%)	*H. pylori* negative (*n*)	*H. pylori* positive (*n*)
Total	708	600	108
Male	316 (45)	255	61
Female	392 (55)	345	47
Platelet count $<100 \times 10^9$/1	23	20	3
Age (mean, in years)	53	53	53
Disease type			
Iron deficiency/anemia	73 (10)	59	14
Malignancy	50 (7)	44	6
Miscellaneous	135 (19)	112	25
Alcohol	6 (1)	5	1
Autoimmune*	69 (10)	63	6
Hepatitis B	6	5	1
Hepatitis C	5	3	2
Transplant recipient**	26 (4)	24	2
Liver disease	15 (2)	10	3
Upper abdominal complaints	317 (45)	271	46

*Patients with celiac disease, imflammatory bowel disease and autoimmune hepatitis. There were no patients in this cohort with ITP.
**Most were kidney transplant patients, a few (<10) patients with a liver transplant were included.

Thrombocyte counts ranged from 18×10^9/l to 789×10^9/l in the disease categories that are known to have an effect on thrombocyte count (specified previously). In the disease categories without known effect on thrombocyte count, thrombocyte count ranged from 110×10^9/l to 726×10^9/l. The last, miscellaneous group, ranges were 69×10^9/l–1059×10^9/l thrombocytes.

Mean difference in white blood cell count was 0.3×10^9/l (95% CI: −0.9 to 0.9) and mean difference in hemoglobin was −0.3 mM/l (95% CI: −1.0 to 0.4), also showing no difference between *H. pylori* infected and *H. pylori* uninfected patients.

All *H. pylori* positive patients underwent eradication therapy with mostly culture-directed therapy (if feasible). Of the 36 *H. pylori* positive patients in whom thrombocyte counts post-eradication were available, platelet counts pre- and post-eradication were 234×10^9/l and 238×10^9/l, respectively, mean difference of −5 (95% CI: −22 to 14).

In the present cross-sectional study including 708 consecutive patients tested for *H. pylori* infection after gastroscopy, we did not find a clear association between thrombocyte count and *H. pylori* status. Also stratified by underlying disease/indication for gastroscopy, no clearly lower thrombocyte count could be shown in *H. pylori* positive patients.

Our primary hypothesis was that *H. pylori* infection might be associated with a lower thrombocyte count, even if the effect might be small. This hypothesis would have supported the idea of an ongoing *H. pylori*-mediated low inflammatory response leading to lower thrombocyte counts. One of the factors that may influence the appearance of thrombocytopenia in the presence of *H. pylori* infection is the presence of the CagA mutation carrying *H. pylori* strains. However, in this cohort, we have not been able to evaluate such an effect. Our study had a power of 0.95 for detecting a difference of 35×10^9 in thrombocyte count with a p value of 0.05. A small effect might therefore been missed.

There are many reports about the link between *H. pylori* infection and ITP. In this cross-sectional study, none of the *H. pylori* positive patients had thrombocyte counts in the range

Table II. Difference in thrombocyte count, between *H. pylori* negative and *H. pylori* positive patients.

	Mean thrombocytes ($\times 10^9$/l) in *H. pylori* negative	Mean thrombocytes ($\times 10^9$/l) in *H. pylori* positive	Mean difference (95% confidence interval)
Total population	257	252	−5 (−23 to 14)
Iron deficiency/anemia	272	266	−2(−64 to 59)
Malignancy	222	186	−32(−117 to 52)
Miscellaneous	272	289	18(−31 to 66)
Alcohol	249	166	−83(−387 to 222)
Autoimmune	272	254	−18(−105 to 67)
Hepatitis B	238	134	−104(not measurable)
Hepatitis C	179	150	29(−129 to 249)
HIV	192	224	33(−151 to 86)
Transplant	205	340	133(−7 to 272)
Liver disease	129	146	−5(−97 to 87)
Upper abdominal complaints	260	253	−1,6(−21 to 18)

*Mean difference adjusted for age and sex.

compatible with a diagnosis of ITP. Although this might suggest that the absolute risk for *H. pylori*-associated ITP is very low, also selection presumably plays a role, since patients with very low thrombocyte counts might not undergo a gastroscopy with biopsies unless the indication is life threatening.

In our study, men were more often *H. pylori* positive than women, most notable in the group with upper abdominal complaints. Although this study was not designed to demonstrate a gender difference in *H. pylori* infection rate, population-based studies and meta-analyses have demonstrated a similar results [9, 10]. So far, the reason for this difference has only been speculated upon.

Our sample was taken from patients mostly with gastrointestinal complaints in a tertiary referral center. Because the prevalence of *H. pylori* infection (15%) did not differ materially from the prevalence in the general population in a recent study in a neighboring country (Belgium), and is a little higher than that reported in a recent large cohort study from the USA [11, 12], our results seem generalizable to the general population.

In conclusion, we could not demonstrate a lower thrombocyte count in *H. pylori* infected patients compared to non-infected subjects. The lack of association between platelet count and *H. pylori* infection in this cohort suggests that the reported association between *H. pylori* and thrombocytopenia is an all or nothing phenomenon that occurs in a small subgroup of patients, if it occurs at all. Since our cohort had relatively few patients with thrombocyte counts $<100\times10^9$, no substantiated conclusion can be drawn.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article. The authors report no affiliation with any organization with a financial interest, direct or indirect, in the subject matter or materials discussed in the article exists.

References

1. Stasi R, Sarpatwari A, Segal JB, Osborn J, Evangelista ML, Cooper N, Provan D, Newland A, Amadori S, Bussel JB. Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: A systematic review. Blood 2009;113: 1231–1240.
2. Arnold DM, Bernotas A, Nazi I, Stasi R, Kuwana M, Liu Y, Kelton JG, Crowther MA. Platelet count response to *H. pylori* treatment in patients with immune thrombocytopenic purpura with and without *H. pylori* infection: A systematic review. Haematologica 2009;94: 850–856.
3. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology 2003;125:1636–1644.
4. Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: A systematic review and meta-analysis. J Antimicrob Chemother 2007;60:237–246.
5. Logan RP, Walker MM. ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of *Helicobacter pylori* infection. BMJ 2001;323:920–922.
6. Jackson L, Britton J, Lewis SA, McKeever TM, Atherton J, Fullerton D, Fogarty AW. A population-based epidemiologic study of *Helicobacter pylori* infection and its association with systemic inflammation. Helicobacter 2009;14:108–113.
7. Terrell DR, Beebe LA, Neas BR, Vesely SK, Segal JB, George JN. Prevalence of primary immune thrombocytopenia in Oklahoma. Am J Hematol 2012;87:848–852.
8. Stasi R, Rossi Z, Stipa E, Amadori S, Newland AC, Provan D. *Helicobacter pylori* eradication in the management of patients with idiopathic thrombocytopenic purpura. Am J Med 2005;118: 414–419.
9. Moshkowitz M, Horowitz N, Beit-Or A, Halpern Z, Santo E. Gender-associated differences in urea breath test for *Helicobacter pylori* infection referrals and results among dyspeptic patients. World J Gastrointest Pathophysiol 2012;3:80–84.
10. de Martel C, Parsonnet J. *Helicobacter pylori* infection and gender: A meta-analysis of population-based prevalence surveys. Dig Dis Sci 2006;51:2292–2301.
11. Sonnenberg A, Genta RM. Low prevalence of *Helicobacter pylori* infection among patients with inflammatory bowel disease. Aliment Pharmacol Ther 2012;35:469–476.
12. Arnold IC, Lee JY, Amieva MR, Roers A, Flavell RA, Sparwasser T, Müller A. Tolerance rather than immunity protects from *Helicobacter pylori*-induced gastric preneoplasia. Gastroenterology 2011;140:199–209.