Research Article

Relevance between *Helicobacter pylori* Infection and Immune Thrombocytopenia

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Abstract

Objectives: This study was conducted to determine: [i] the prevalence of *Helicobacter pylori (H. pylori)* infection in adult patients with immune thrombocytopenia (ITP), [ii] the response of *H. pylori* infected ITP patients to eradication therapy of *H. pylori*, [iii] an anticipating factor for platelet response in *H. pylori*-infected ITP patients.

Methods: The study enrolled 60 adult patients diagnosed with ITP recruited to the Outpatient Clinic of Haematology, Oncology Center of Mansoura University (OCMU), Mansoura, Egypt. *H. pylori* infection was detected by faecal *H. pylori* antigen enzyme linked immunosorbent assay (ELISA). Serum *H. pylori* anti-cytotoxin associated gene A (anti-CagA) IgG titers were assessed by ELISA. ITP patients positive for *H. pylori* infection received standard eradication regimen.

Results: *H. pylori* infection was detected in 33.3% of ITP patients. 13 patients (65%) exhibited an increased platelet count safter eradication therapy (treatment responders). The decline in the titers of anti-CagA IgG after therapy was statistically significant in responders ($p = 0.005$) compared to non-responders ($p = 0.1$).

Conclusion: *H. pylori* detection and eradication is recommended in adult patients with ITP, so that farther harsh treatment approaches of ITP could be adverted in infected patients. Moreover, anti-CagA IgG titer is a predictive indicator for platelet recovery after eradication therapy.

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Introduction

Immune thrombocytopenia (ITP), first described by *P.G.Werlhof*[1], is the most common autoimmune haematologic disorder, affecting individuals of all genders, races and ages[2]. The former designation "idiopathic" was coined because in most of cases, the underlying aetiology was mysterious. However, in recent decades, the list of aetiologies of ITP has been canonically increasing, so the term "idiopathic" is becoming outdated, and instead replaced by "immune" thrombocytopenia[3]. The disease is mediated by anti-platelet autoantibodies that bind to platelets and megakaryocytes, enhancing platelet destruction by the reticulo-endothelial system (RES) and suppressing megakaryopoiesis. Most of these antibodies are directed against platelet membrane glycoprotein (GP) complexes; GPIIb/IIIa or GPIbIX[4].

In adults, ITP typically has an insidious onset, with no preceding viral or other illness and has a chronic course. The symptoms and signs of ITP in adult patients are highly diverse and range from the fairly common asymptomatic patient with mild bruising and mucosal bleeding (e.g. oral or gastrointestinal tract) to frank haemorrhage from anybody site, the most catastrophic of which is intracranial[5].

Helicobacter pylori is a Gram-negative, microaerophilic, spiral-shaped, flagellated bacterium that colonizes the human gastric mucosal layer[6]. This bacterium was first isolated from gastric biopsy by *Robin Warren* and *Barry Marshall* in 1984[7]. *H. pylori* has been implicated in the aetiology of a spectrum of gastrointestinal diseases, including; peptic ulcer disease, gastric cancer and MALToma (mucosa-associated lymphoid tissue lymphoma)[8]. In addition to gastric disorders, this pathogen is associated with various non-gastrointestinal-related illnesses such as ITP, coronary artery disease, Alzheimer's disease, iron deficiency anaemia, as well as a variety of autoimmune disorders[9].

The pertinence between *H. pylori* infection and ITP was first reported in 1998, by an Italian group who perceived a

marked increase in the platelet count in 8 out of 11 patients after receipt of eradication therapy[10]. Subsequently, other co-workers revealed that eradication of *H. pylori* infection among patients with ITP resulted into a substantial and steady increase in the platelet count in more than half of the treated patients[11]. However, other investigators yielded contradictory results regarding restoration of platelet counts in ITP patients after achievement of *H. pylori* eradication[12].

The cytotoxin-associated gene A (CagA) protein, the product of the *CagA* gene, is one of the major *H. pylori* virulence factors. Currently, CagA positive *H. pylori* strains are proposed to play a role in the pathogenesis of ITP. It is postulated that molecular mimicry between *H. pylori* CagA protein and various platelets' glycoprotein antigens could induce anti-glycoprotein auto-antibody production that cross react with host platelets[13].

Accordingly, this study was undertaken to: (i) verify the prevalence of *H. pylori* infection in adult patients with ITP, (ii) interrogate the impact of *H. pylori* eradication therapy on platelet counts among enrolled patients with *H. pylori*-associated ITP, (iii) find out a prognostic factor for platelet recovery in *H. pylori*-infected ITP patients.

Subjects and Methods

This is a prospective cohort study, conducted over a period of 12 months starting from October 2014 to September 2015.

Subjects

The study included 60 consecutive patients (22 males and 38 females; 1:1.7) newly diagnosed with ITP who attended the Outpatient Clinic of Haematology, Oncology Center of Mansoura University (OCMU), Mansoura, Egypt. The inclusion criteria included patients > 18 years of age diagnosed with ITP according to American Society of Haematology[14] criteria based on an initial platelet count < 100 x 10³/μL. To avoid the confusing effect of incident ITP therapies, patients were eligible for the study if they had a platelet count above 20 x 10³/μL and below 100 x 10³/μL, and did not require treatment for thrombocytopenia for at least 3 months before their inclusion. A bone marrow examination was performed in all patients to rule out other causes of thrombocytopenia.

Patients with other causes of thrombocytopenia such as HCV, HBV, or HIV infections, drugs, lymphoproliferative disorders, autoimmune disorders and pseudothrombocytopenia had been excluded. Furthermore, patients who had active life threatening bleeding at the time of recruitment were excluded.

Detection of *H. pylori* infection

Helicobacter pylori infection was determined by detection of *H. pylori* antigens in stool specimens through faecal *H. pylori* antigen enzyme linked immunosorbent assay (ELISA) kit. Assay procedure was done as per manufacturer's instructions [AccuDiag™, Inc., USA]. The optical density (OD) of each well was read at 450 nm on a microwell reader.

Detection of *H. pylori* anti-CagA IgG

Sera were obtained from *H. pylori*-infected patients with ITP and stored at -20 °C until serological testing was done. An ELISA kit was used and the procedure was done according to the manufacturer's instructions [RADIM, Italy].

Helicobacter pylori eradication therapy

Patients who had *H. pylori* infection were given standard triple eradication regimen for *H. pylori* comprising; amoxicillin 1000 mg twice daily, clarithromycin 500 mg twice daily and pantoprazole 40 mg twice daily for 1 week. On the other hand, patients without *H. pylori* infection received no eradication therapy and were followed up as a control group. Serum levels of anti-CagA IgG were assessed before and after therapy to demonstrate the significant correlation of titer decline and response.

Monitoring

Platelet counts were assessed at the time of testing (baseline), then 2 and 6 months after completion of treatment. Success of eradication of *H. pylori* infection was determined by repetition of *H. pylori* faecal antigen testing 4 weeks after treatment withdrawal. The clinical response to treatment was defined according to the guidelines of the International Working Group (IWG) on ITP[15].

Statistical analyses

All Statistical analyses were performed by using IBM SPSS 22.0 software version for windows (SPSS, Inc., Chicago, IL, USA). Data were expressed as either the number (percentage) or median (range). The Mann-Whitney test was used to compare means between 2 groups. The Kruskal-Wallis test was used to compare the mean platelet counts between groups during the follow up period. Fisher's exact test was used to analyze the statistical significance associated with anti-CagA IgG presence. The differences as regard to anti-CagA IgG before and after therapy were analyzed using the Wilcoxon's test. *P* values of < 0.05 were considered to be statistically significant.

Study power calculation

As the prevalence of *H. pylori* infection in adult patients with ITP was the primary outcome of this research, study power was calculated online (www.dssresearch.com) using the sample percentage (33.3%) and considering the worst acceptable value as 30.3%, the sample size was 60 with 95% confidence level. The study power was found to be 8.6% which is low due to small sample size.

Results

The present study involved 60 consecutive patients newly diagnosed with ITP (36.7% males and 63.3% females) with age ranging between 29 and 59 years (median age; 45 years). The median disease duration for the involved subjects was 6 months (ranging from 3-12 months). The median baseline platelet count was 34 × 10³/μL (23 - 67 × 10³/μL). The most common clinical manifestation was petechiae (52.9%), followed by gum bleeding (38%), menorrhagia (32.4%) and epistaxis (12.9%). *H. pylori* infection was detected in 20 out of the 60 ITP patients (33.3%) by faecal *H. pylori* antigen ELISA kit. [The patients' baseline characteristics are shown in table 1].

Table 1: Baseline characteristics of the study participants.

Variable	Result
Median age (range):	45 years (29 - 59)
Gender (%):	
-Male	22 (36.7%)
-Female	38 (63.3%)
Median disease duration (range):	6 months (3 - 12)
Clinical presentations:	
-Petechiae	52.9%
-Gum bleeding	38%
-Menorrhagia	32.4%
-Epistaxis	12.9%
***H. pylori* infectivity (%):**	
-Positive	20 (33.3%)
-Negative	40 (66.7%)
Median baseline platelet counts (x 10^3/ µL): (range):	34 (23 - 67)
Concomittant treatment (%):	
-Corticosteroid therapy	3 (5%)
-Splenectomy	0 (0%)

Legend: Data are expressed as either the number (percentage) or median (range).
Abbreviations: *H. pylori: Helicobacter pylori.*

In the current work, no significant difference (p = 0.5) was noticed in the baseline platelet counts between the *H. pylori* negative group (n = 40), *H. pylori*-positive-treatment responder group (n = 13) who exhibited complete response (CR) to eradication therapy [as per IWG criteria] and the *H. pylori*-positive-treatment non-responder group (n = 7). However, 2 months after eradication therapy, the platelet counts increased significantly from 34 (29 - 51) × 10^3/µL to 10^3 (100 - 123) × 10^3/µL in the *H. pylori*-positive-treatment responder group (*p* = 0.0001) in comparison to that of the *H. pylori*-positive-treatment non-responder group (*p* = 0.01) and to the *H. pylori* negative group (*p* = 0.01). Furthermore, 6 months after eradication therapy, the platelet counts displayed a significant increase in the treatment responder group in comparison to the treatment non-responder group and the *H. pylori* negative group (*p* = 0.0001) [values are mentioned in table 2]. In addition, the platelet recovery was sustained over the follow-up period.

Concerning the presence of anti-CagA IgG in the *H. pylori*-infected patients as determined by ELISA, a significant difference was observed between both treatment responders and treatment non-responders [92.3% versus 71.4% respectively; *p* = 0.01]. It is worth mentioning that the initial titers of anti-CagA IgG were significantly higher in ITP patients responding to *H. pylori* eradication compared to the non-responding group [69 relative unit (RU)/mL (63 - 78) *versus* 38 RU/mL (36 - 40); *p* = 0.01] (Figure 1). Moreover, the decline in the titers of anti-CagA IgG after eradication therapy was statistically significant in the treatment-responders (*p* = 0.005) in comparison to the non-responders (*p* = 0.1) as determined by the Wilcoxon's test [values are shown in table 2].

Table 2: Comparison of the patient's characteristics between *H. pylori*-positive-treatment responders, *H. pylori*-positive-treatment non-responders and *H. pylori* negative group

	H. pylori positive (N= 20)		*H. pylori* negative (N= 40)	P-value
	Treatment responders (n= 13)	Treatment non-responders (n= 7)		
Age in years (range):	35 (29-57)	44 (34-59)	47 (31-58)	0.2
Gender: (Male: Female)	8 males: 5 females	2 males: 5 females	12 males: 28 females	0.2
Disease duration in months: (range)	6 (4 - 12)	6 (4 - 7)	6 (3 - 12)	0.4
Platelet counts (×10^3/ µL): Baseline	34 (29 - 51)	37 (29 - 51)	33.5 (23 - 67)	0.5
Platelet counts (×10^3/µL): 2 months after therapy	103 (100 - 123)	53 (45 - 62)	68 (45 - 112)	0.004*
Platelet counts (×10^3/µL): 6 months after therapy	157 (106 - 176)	63 (57 - 76)	89.5 (64 - 157)	0.0001*
Anti- CagA IgG (Baseline):	12 (92.3%)	5 (71.4%)	ND	0.01**
Anti-CagA IgG titer [RU/mL] (Baseline):	69 (63 - 78)	38 (36 - 40)	ND	0.01***
Anti-CagA IgG titer [RU/mL] (After therapy):	40 (28-44)	31 (30-35)	ND	0.1

Legend: Data are expressed as median (range) or number (percentage).
* Kruskal-Wallis test.
**Fisher's exact test.
*** Mann-Whitney test.

Abbreviations: *H. pylori*: *Helicobacter pylori*; Anti-CagA: anti-cytotoxin associated gene A; RU/mL: relative unit/mL; ND: not determined.
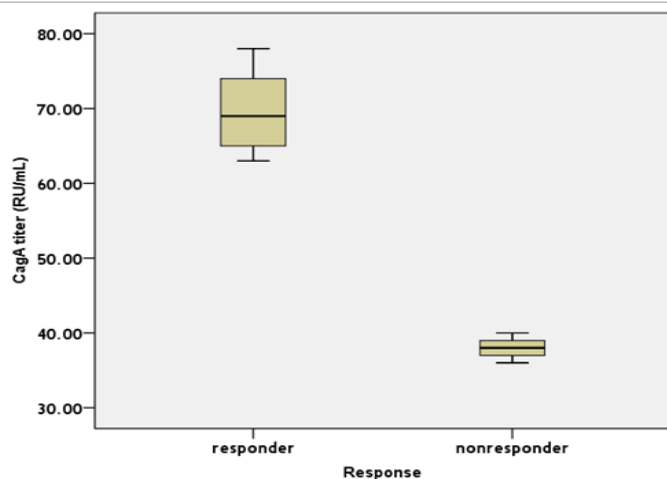
Figure 1. The titers of anti-CagAIgG before eradication therapy in *H. pylori*-infected ITP patients. The ELISA titers of serum anti-CagAIgG in the responder group were significantly higher than those in the non-responders (p = 0.01). Values represent the median (range) expressed in RU/mL (relative unit/mL).

Discussion

The pathogenesis of *H. pylori*-associated ITP is still ambiguous, although several hypotheses have been proposed. One is that *H. pylori* components may mimic the molecular make-up of platelet antigens, so antibodies to *H. pylori* components may cross react with platelet surface antigens[16].

In the present work, the prevalence of *H. pylori* infection in ITP patients was 33.3% (20 out of 60 ITP patients). This finding is compatible with that reported by Hwang., *et al* (2016) where *H. pylori* infection was detected in 41.1% of their involved group[17], even though lower rates were published in other studies accounting for 22% and 11.1%, respectively[18,19]. It seems that diverse racial, industrial and social conditions prevailed in the studied populations could contribute to such disparity.

Although some authors claimed higher prevalence of *H. pylori* infection among younger patients[13] and others reported predominance of infection among older patients[20], our study realized no significant difference attributed to age distribution which is in common to other investigators[21]. Additionally, the gender distribution between our groups was similar (p = 0.2), comparable to what mentioned by other co-workers[22]. Besides, no statistically significant difference was detected between *H. pylori*-infected group and non-infected group in terms of duration of ITP (p = 0.5) which is concomitant with an earlier review[23].

In the existent work, out of the 20 *H. pylori*-infected ITP patients, 65% showed complete platelet response (CR) to eradication therapy of *H. pylori* (designated as responder group), whereas 35% were non-responders [as per IWG criteria]. Similarly agreeable results were described by several Japanese groups including; Hino., *et al* (2003)[24], and Asahi., *et al* (2006) [25]. Likewise, an earlier Italian report by Emilia., *et al* (2002) informed 66.7% response rate to eradication regimen[26]. Nonetheless, Campuzano-Maya (2007) yielded a higher platelet response up to 80.8% from a retrospective study carried out in Colombia (Latin America)[27]. The high rate deduced from this retrospective study could be ascribed to recall bias or selection bias, unlike the results of prospective trials. Recently, Chey., *et al* (2017) accomplished a systematic review of 25 studies, all of which encompassed at least 15 adult patients. Consequently, they inferred that platelet counts in ITP patients displayed a significant rise after *H. pylori* eradication therapy[28]. Also, Franchini. *et al* (2017) suggested that the eradication of *H. pylori* in infected patients with ITP will safeguard those patients from other aggressive and prolonged treatment options[29].

In contrast to our study, several researchers have rebutted a significant link between *H. pylori* and ITP. For example, Jarque., et al (2001), from a study conducted in Spain, concluded that only 3 out of 23 (13%) patients with ITP in whom *H. pylori* was eradicated experienced a significant increase in the platelet count[30]. Furthermore, Michel and colleagues (2004) disclosed that only one out of 14 North American ITP patients who responded to *H. pylori* eradication had a rise in platelet count[31]. Ahn., *et al* (2006), too, described a poor response to *H. pylori* eradication therapy in patients with ITP in the United States accounting only for 6.7%[32].

The discrepancy among different groups regarding the response to *H. pylori* eradication therapy among ITP patients could be attributed to several reasons. Firstly, a positive correlation is established between the prevalence of *H. pylori* infection and the platelet response through which the response rate is higher in countries with higher prevalence of *H. pylori* infection like Japan[24,25] and Latin America[27,33]. On the contrary, studies performed in North America announced poor response rate to eradication treatment that parallel the low prevalence of *H. pylori* infection[31,32]. Secondly, variation in the patients' characteristics including their genetic constitution, could also contribute to the discordant outcomes of eradication therapy in these studies. Lastly, the infecting strains of *H. pylori* and their virulence determinants, such as CagA expression might induce variability in ITP response to *H. pylori* eradication.

The present data demonstrated that ITP patients responsive to *H. pylori* eradication had initially higher titers of anti-CagA IgG compared to non-responsive group (p = 0.01). Moreover, the decline in the titers of anti-CagA IgG after eradication therapy was statistically significant in the treatment-responders (p = 0.005) in comparison to the non-responders (p = 0.1). That being the case, the difference in the anti-CagA IgG status could be used as a predictor of platelet response to eradication therapy of *H. pylori*. In accordance with our results, Suzuki., *et al* (2005) mentioned that among patients with ITP, the titers of anti-CagA IgG were significantly higher in responders than in non-responders (p = 0.04)[34]. Furthermore, Kodama., *et al* (2007) reported a significant reduction in the titer of anti-CagA IgG after eradication therapy in the responder group compared to the non-responders. They proposed that the immune response of the patients to CagA protein may be prolonged after *H. pylori* eradication in the non-responders[35].

Conclusion

Globally, the results of this study affirmed that *H. pylori* eradication has a positive impact on platelet counts in adult patients with ITP. Thereby, we endorse initial screening of all ITP patients for *H. pylori* infection and considering eradication therapy for the infected patients. Currently, most of the available treatment modalities of ITP are costly, together with undesirable

adverse effects. On the other hand, *H. pylori* eradication therapy is economical with tolerable side effects. So, this strategy will be beneficial particularly in developing countries like ours. Additionally, we advocate routine inquiry for serum titers of anti-CagA IgG in those patients as a prognostic marker for platelet recovery after eradication therapy.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical approval: The protocol of this study was reviewed and approved by our institutional review board (R/16.05.85). All procedures were performed in accordance with the ethical standards of the institutional research committee and with Helsinki declaration.

Informed consent: Informed consent was obtained from all participants included in this study.

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