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RESEARCH ARTICLE

HELICOBACTER PYLORI ERADICATION TREATMENT EFFECTS ON PLATELET VALUES IN THE REFRACTORY ITP SPLENECTOMY PATIENTS

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ABSTRACT

Background and Aims: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune blood disorder with a characteristic purpuric rash and thrombocytopenia. The disease can progress into chronic ITP when steroid treatment fails. A quarter of patients who had splenectomy due to chronic ITP may continue to have thrombocytopenia. In these cases, it is thought that testing positive for *H. pylori* may be perpetuating thrombocytopenia.

Methods: We investigated the presence of *H. pylori* infection in patients with chronic ITP who are either responsive or refractory to splenectomy using invasive GI endoscopy followed by rapid urease test.

Results: We report that chronic ITP patients who were refractory to splenectomy had improved platelet counts following the eradication of *H. pylori*

Conclusions: We suggest screening for *H. pylori* in patients with chronic ITP refractory to splenectomy. Treatment of H. pylori can increase the response to splenectomy as judged by the increased platelet counts.

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INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP), more recently as immune thrombocytopenic purpura, is an autoimmune disorder characterized by isolated destruction of peripheral thrombocytes. While the specific causes of ITP are not known, abnormalities in megakaryocytopoiesis have been implicated as causative factors (Scandellari *et al*., 2009). In an effort to standardize the terminology and definition of ITP, a panel of experts published guidelines in which a platelet count of less than 100 X 109 was established as the threshold for diagnosis (Rodeghiero *et al*., 2009). According to the suggested terminology, patients with bleeding symptoms at time of presentation or occurrence of new bleeding symptoms requiring additional therapeutic intervention are classified as "severe ITP", whereas patients who have failed to respond to splenectomy and have severe ITP are classified as "refractory ITP" (Rodeghiero *et al*., 2009).

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In ITP, increased platelet clearance results from the response of the immune system against thrombocyte membrane proteins, which become auto-antigenic. Platelets are destroyed by macrophages in the spleen and auto-antibodies are produced that target thrombocytes and megakaryocytes, which are then attacked by cytotoxic T-cells (Veres *et al*., 1999). Studies have revealed the presence of antibodies against the platelet antigen GPIIb/IIIa in the plasma of patients with ITP (Suvajdzic *et al*., 2006). ITP is more prevalent among children and young women, and in general presents itself after upper respiratory system infections. While ITP symptoms in children can resolve spontaneously, in adults it can progress into chronic ITP, in which steroid treatment is not successful. The incidence of ITP in adults is about 1.6-3.9 per 100,000 persons per year (Saltzman *et al*., 2010). Diagnosis of ITP is made on the basis of exclusion of other causes such as autoimmune diseases, infections, pregnancy, immune deficiency, blood transfusions, and presence of solid tumors (ITP, 2011). In adults, first line treatment of ITP is considered if the patient's platelet count is below 30 X 109 or, with platelet count above 30 X 109 yet have the risk of bleeding or indication of bleeding (ITP, 2011; Provan *et al*., 2009; Neunert *et al*., 2010). Corticosteroids are

preferred drugs of the first-line therapy. Intravenous immunoglobulin (IVIg) treatment is recommended when a rapid response is desired. Intravenous anti Rh D is another alternative for ITP patients who have not undergone splenectomy or do not have autoimmune hemolytic anemia. When none of the first line treatments are successful, second-line therapy options are applied. Splenectomy is generally the first choice of treatment at this step. 80% of patients respond well to splenectomy of which one-fifth may not achieve a long lasting response.

70% of patients with chronic ITP respond to splenectomy. The remaining thirty percent continue to have thrombocytopenia and related symptoms (Weiss, 1990). The correlation between *H. pylori* infection and ITP remains controversial. Studies by Japanese and Italian groups Stasi *et al.* and Tsumoto *et al.*) reported positive outlook concomitant with the eradication of *H. pylori*, however there has been other reports in the field that indicated otherwise (Stasi *et al*., 2009; Tsumoto *et al*., 2009). In chronic ITP cases where the platelet count was below 30 X 109, eradication of *H. pylori* had no benefit. Nonetheless, due to the availability of affordable *H. pylori* treatments, in recent guidelines eradication treatment is recommended. *H. pylori* screening is done by urea-breath and stool tests (Stasi *et al*., 2009; Tsumoto *et al*., 2009). In this study we aimed to investigate the incidence of *H. pylori* infection among chronic ITP patients who are not responsive to splenectomy. We have also compared the effect of other parameters, such as age, gender as well as eradication of *H. pylori* on the platelet count.

METHODS

Definition of the cohort

All subjects included in this study were patients admitted to the Marmara University Training and Research Hospital from January 2000 to December 2009. We first identified the patients who had splenectomy due to ITP. We also included patients who had refractory thrombocytopenia post-splenectomy. For the purpose of this study, we excluded patients who did not respond to splenectomy and were on non-steroid drug treatment. We have also excluded cases in which the patient still had residual spleen due to incomplete surgery. Demographics, patient history, prior treatments and laboratory test results were recorded. Specifically, gender, age at the time of diagnosis, date of surgery, occurrence of ITP in the family, use of corticosteroids, platelet counts before and after *H. pylori* eradication were included.

Medical tests

Upper gastrointestinal (GI) endoscopy was performed on a total of 38 ITP patients, including cases with either refractory or non-refractory splenectomy. Prior to the endoscopy, platelet counts of fasting patients were measured and recorded. A single endoscopy specialist performed all GI endoscopy procedures using the Olympus brand gastroscope (CV-145, Tokyo, Japan). There was no incidence of complication and each procedure lasted on average 11 minutes. All patients received the same amount of sedative drug (Midazolam 0.05 mg/kg). To test for the presence of *H. pylori*, during endoscopy, biopsy samples were obtained fromthe prepyloric antrum and incisura angularis. These biopsy samples were subsequently used in the rapid urease test.

Statistical analysis

Data analysis was performed using the SSPS software. Non-parametric models were used to fit data. To compare the refractory and responsive groups, we used the Mann-Whitney test, whereas to compare the ratios, chi-square test was used.

RESULTS

The cohort consisted of 38 patients who were diagnosed with ITP and failed to respond to the first line of drug treatments, and therefore had splenectomy. 20 of these patients responded to the splenectomy, whereas 18 did not. We compared the age of these two groups and tested to see if there is any significant difference. Based on Mann-Whitney test we found that the group that responded splenectomy had an average age of 39.1 (±13.86), while the other group, which was refractory to splenectomy had an average age of 39.8 (±14.61) with a p-value of 0.671. We concluded that there are no statistically significant differences with regards to age between the two groups of patients that were either responsive or non-responsive to splenectomy. Next we compared the gender differences of the two groups using the chi-square test.

We found that similar to the age factor, there was no significant difference in gender between the two groups of patients (p= 0.299). We also compared the duration of corticosteroid use and platelet counts between the responsive and non-responsive groups. We found that the non-responsive group had lower platelet count (Mann-Whitney, p=1x10-5) and the length of the steroid treatment was also longer (Mann-Whitney, p=1x10-6) (Table 1).

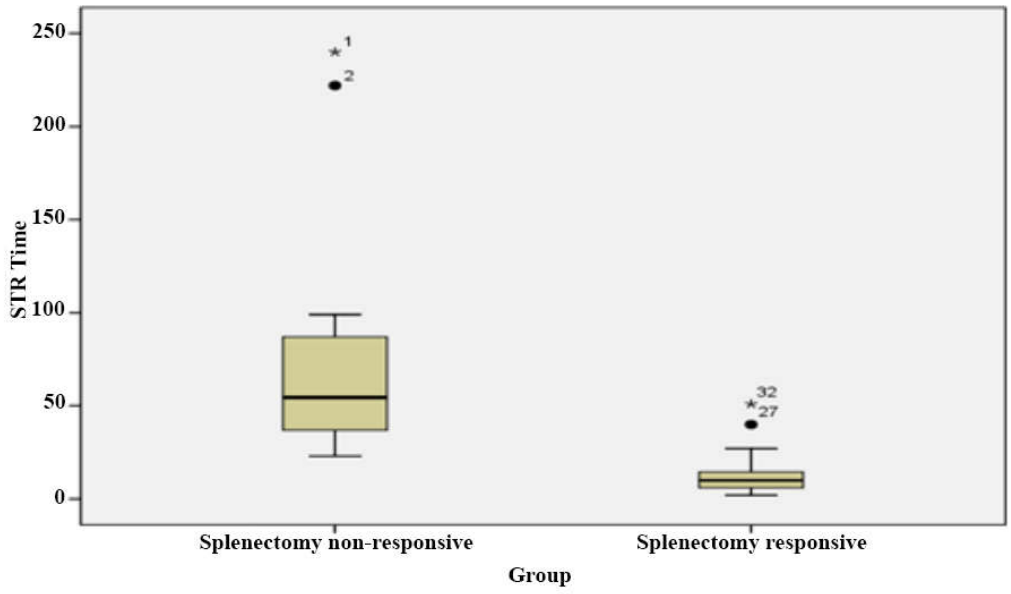
We then compared the level of *H. pylori* existence in the responsive and non-responsive groups. We found that the non-responsive group of patients tested significantly more positive for the presence of *H. pylori* than the responsive group (Chi-square test, p=0.006) (Table 2). When we examined the platelet counts of the non-responsive group after *H. pylori* eradication, we found that the platelet levels were significantly increased compared to the pre-treatment levels (Wilcoxon signed-rank test, p=1x10-7) (Table 3).

DISCUSSION

Here, we showed that chronic ITP patients who were refractory to splenectomy had improved platelet counts following the eradication of *H. pylori*. The positive effect of *H. pylori* eradication on platelet counts in patients with ITP is a controversial issue. In the USA and Canada, where prevalence of *H. pylori* is low, studies showed no association between testing positive for *H. pylori* and having chronic ITP (Jackson, 2008). In contrast, in countries such as Japan and Italy where the prevalence of *H. pylori* is high, it was reported that there is a positive relationship between *H. pylori* infection and chronic ITP and eradication of *H. pylori* had improved the platelet counts in patients with chronic ITP (Tsumoto *et al*., 2009).

Table 1. Steroid using-Platelet count (PLT count) values comparison in the splenectomy respon and non-respond groups

	Group	N	Average	Standart deviation
Steroid-use date (Month)	Splenectomy non-responsive	18	74.3	61.8
	Splenectomy responsive	20	13.5	12.5
PLT count	Splenectomy non-responsive	18	80000.0	38624.9
	Splenectomy responsive	20	286000.0	75715.5



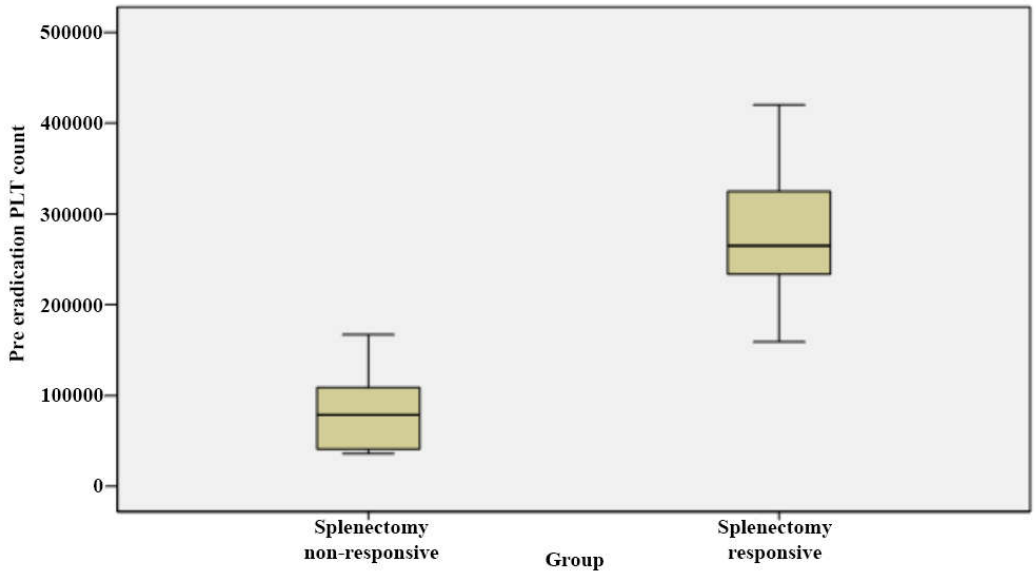


Table 2. *H.pylori*-positive comparison in the splenectomy respond and non-respond groups

			Group		
			Splenectomy non-responsive	Splenectomy responsive	Total
H.pylori	Off	n	1	9	10
		%	5.6%	45.0%	26.3%
	On	n	17	11	28
		%	94.4%	55.0%	73.7%
Total		n	18	20	38
		%	100.0%	100.0%	100.0%

Table 3. Pre and post eradication of *H. Pylori*'s platelet countin the splenectomy non-respond group

Group		N	Minimum	Maximum	Average	Standart deviation
Splenectomy non-responsive	**Pre eradication PLT Count**	18	36000.0	167000.0	80000.0	38624.9
	Post eradication PLT Count	18	48000.0	239000.0	128444.4	55724.3

Our study differs from others in the field in that we investigated the presence of *H. pylori* using upper GI endoscopy procedures in patients who had splenectomy due to ITP. We found that the patients in the responsive group were less likely to have *H. pylori*, whereas the number of patients in the non-responsive group tested positive for *H. pylori* infection significantly more than the responsive group. We also compared age as a covariate in this study, however did not find age to be a significant factor. This is in agreement with studies previously reported, including the one by Stasi and colleagues, in which they reviewed 25 publications involving 1555 subjects and did not report any association with age (Stasi *et al*., 2009). In our study, the responsive group had ten female and ten male subjects, whereas the refractory group had twelve female, six male subjects.

It is thought that ITP is more common among women, however our analysis did not find any gender bias. Consistently, in a Japanese study by Tsumoto and colleagues did not observe any significant association between the occurrence of ITP and gender (Tsumoto *et al*., 2009). We showed that the patients refractory to splenectomy with concomitant *H. pylori* infection had lower platelet counts prior to the eradication of *H. pylori* and the counts improved significantly after treating the *H. pylori* infection. Study by Suvajdzic and colleagues investigated the rate of *H. pylori* positivity in 54 patients with chronic ITP using the urease test and found that compared to the Serbian population average, patients with chronic ITP had higher incidence of *H. pylori* infection (Suvajdzic *et al*., 2006). The patients in our study who has chronic ITP also had higher incidence of *H. pylori* infection compared to the Serbian population average (90% versus 65% Serbian population average).

In the same study by Suvajdzic, they were able to treat *H. pylori* infection in 77% of the patients. We, on the other hand, were able to treat 88% of our patients with *H. pylori* infection. Suvajdzic and colleagues observed that in 26% of the patients after eradication of *H. pylori*, the platelet counts had improved and were stable for 18 months. In two patients they observed complete remission. In the case of our study, we observed higher platelet counts in 55% of the patients. However, we were not able to record the how long these patients preserved their improved platelet counts or how many of them had complete remission. Suvajdzic and colleagues also observed that patients with which *H. pylori* eradication was not successful, there was not improvement in their platelet counts. Similarly, in our study we did not observe meaningful differences in platelet counts of patients with unsuccessful *H. pylori* eradication (Suvajdzic *et al*., 2006). Study by Tsumoto and colleagues investigating 30 patients with chronic ITP, including those they followed for 7 years, they found that 70% of patients had *H. pylori* infection. In 20 of those patients, after *H. pylori* eradication, within one month they reported improved platelet counts. 45% patients (9 individuals) were followed for 7 years. During this time 8 of them stayed in complete remission without need for additional therapy, and one of them had reoccurrence of ITP and was given steroids. In the same report, 9 patients that are in the no *H. pylori* infection group were still treated for the infection, with no positive outcome in platelet counts (11). These findings are in line with our study presented here, in which we also found significant associations with *H. pylori* eradication and improved platelet counts post *H. pylori* treatment. In the future, it will be interesting to establish new studies in which we would follow the duration of remission in these patients. Here, we also investigated chronic ITP patients who have undergone

splenectomy and platelet counts of these patients after the eradication of *H. pylori*. Or results are similar to the findings of Scandellari and colleagues, in which they investigated the relationship of *H. pylori* infection and chronic ITP in patients non-responsive to splenectomy (1). Taken together, we suggest triple treatment regimen for chronic ITP in patients non-responsive to splenectomy. This regimen consists of splenectomy, cyclosporin dosage and *H. pylori* eradication. In sum, we investigated the presence of *H. pylori* infection in patients with chronic ITP who are either responsive or refractory to splenectomy using invasive GI endoscopy followed by rapid urease test. Our study is unique in that compared to similar studies in the field we used GI endoscopy to test for *H. pylori* infection.

Our study has certain pitfalls. We have not investigated the secondary disorders that may have been present in the patients who are either in the responsive or non-responsive splenectomy group. It is possible that presence of other related disorders could have caused thrombocytopenia. Also, we did not investigate the drug treatments that the patients were on but had stopped prior to the upper GI endoscopy. This information could have been beneficial in terms of drug selection for the *H. pylori* eradication therapy. Indeed, we were not successful in treating the two patients who were in the non-responsive group for *H. pylori.* These patients were excluded from our analysis.

Conclusion

In this study, we showed that patients with ITP who are refractory to splenectomy tested positive for *H. pylori* more often than the control group. After *H. pylori* eradication, we observed higher platelet counts in patients with refractory to splenectomy. As such, we recommend screening for *H. pylori* in patients with chronic ITP refractory to splenectomy. Treatment of *H. pylori* can increase the response to splenectomy as judged by the increased platelet counts.

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