

Frequency of Helicobacter Pylori Infection in Immune Thrombocytopenia

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ABSTRACT

Objective: To accomplish the comparative analysis of clinical features and laboratory findings in Helicobacter Pylori positive and negative patients with Immune thrombocytopenia.

Patients and Methods: This cross sectional study was conducted from May 2013 to Nov 2014 at Hematology Unit, Liaquat National Hospital, Karachi. During the study duration, 59 adult patients, diagnosed as chronic immune thrombocytopenia were enrolled in the study. Helicobacter Pylori infection was documented by Helicobacter pylori stool antigen (HpSA) enzyme immunoassay method (EIA). Frequencies were calculated. Chi-square test and independent sample t test were used for comparison. P-value of less than 0.05 was considered statistically significant.

Results: Helicobacter Pylori infection was detected in 25 out of 59 cases of chronic immune thrombocytopenia. No statistically significant differences were seen in H-Pylori positive and negative patients with respect to clinical features and laboratory findings except mean platelet count, which was lower (57.95 ± 15.1) in Helicobacter Pylori negative as compared to positive patients (71.44 ± 18.8).

Conclusion: We found no significant difference between the clinical and laboratory attributes in H Pylori positive and negative cases. Significant finding of high platelet count in Helicobacter Pylori positive patients, may perhaps narrate the possible association.

Key words: Chronic Immune thrombocytopenia, Helicobacter Pylori, Platelet count.

Author's Contribution

¹ Conception, synthesis, planning of research and manuscript writing Interpretation and discussion

² Data analysis, interpretation and manuscript writing, ³ Active participation in data collection.

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Introduction

Immune Thrombocytopenic Purpura (ITP) is an acquired immune condition defined by a low platelet count secondary to rapid platelet destruction by autoantibodies against platelet.^{1, 2} ITP is diagnosed as decreased platelets on the blood smear and the exclusion of other causes of thrombocytopenia.^{1, 2} As ITP is caused by anti-platelet antibodies, the reason of the autoimmune disease remains enigmatic. Several immunological studies have still not explained why some persons generate anti-

platelet antibodies leading to ITP, while the great majority of people do not. The yearly incidence of adult ITP ranges 1.6-3.9 per 100,000 per year.² The assessed female-to-male ratio ranges between 1.2-1.9.²

ITP is classified based on the presence or absence of other underlying diseases (primary or secondary), patient age (adult or childhood ITP) and duration of thrombocytopenia (acute, persistent or chronic).² ITP in adults commonly is chronic in nature and progresses

insidiously, seen mostly in females and less likely resolves spontaneously.² Conversely adult ITP commonly occurs without a clear provoking event and mostly leads to chronic disease and patient may present with moderate to severe bleeding¹. Chronic ITP is more commonly seen in older people being twofold greater in people older than 60 years, and rises with time.³ Gender variance disappears with progression of age.³

Immune thrombocytopenia may follow secondarily in certain infectious diseases, lymphoproliferative diseases, autoimmune disorders and drugs.⁴ Among the infections, Helicobacter Pylori is an important etiological factor as its existence can cause the persistence of disease.⁵

The aim of this study was to determine the frequency of Helicobacter pylori infection in adult ITP patients and secondly to compare the clinical and laboratory aspects between positive and negative patients with ITP. As local published data is limited on this disease and it may be anticipated that frequency might be different in our population as compared to international studies. Study will be beneficial as patients could be offered eradication therapy if deemed appropriate.

Patients and Methods

This cross sectional study was conducted in Hematology Unit, Liaquat National Hospital, Karachi. Calculated sample size was 55 by using confidence interval 95%, precision 10% and prevalence 83%.⁷ To overcome the possibility of dropouts we enrolled 59 adult patients suffering from ITP by non-probability consecutive technique. Study duration was 19 months from May 2013 to Nov 2014. Patients with more than six months history of bleeding with thrombocytopenia or asymptomatic thrombocytopenia with platelet count below $150 \times 10^9/L$ were enrolled. Patients recently treated for H-pylori eradication therapy, history of malignancy or chronic liver disease and those who were on medication known to cause thrombocytopenia were excluded. Bone marrow failure, disseminated intravascular coagulation and patients with hypersplenism were also excluded. An informed consent was taken from each enrolled patient. Patient's history and physical examination was conducted. After thorough clinical evaluation, stool samples were collected in a plain container. Antigen of H-pylori was detected from stool sample by immunoassay

methodology. Results were reported as positive or negative. The specificity and sensitivity of the test were 96% and 83% respectively. Confounding variables and bias were controlled by following the strict exclusion criteria. Data was compiled and analyzed through Statistical Package of Social Sciences (SPSS) version 13. Mean \pm SD was calculated for the quantitative variables i.e. age, platelet count, hemoglobin, hematocrit, MCV, MPV and WBC count. Frequency and percentages were calculated for qualitative variables i.e. gender and outcome (H-pylori antigen). Chi-square test was used to analyze association between qualitative variables. Independent t-test was used to determine significant difference in quantitative variables. P-value < 0.05 was considered as statistically significant.

Results

Out of 59 patients, 36 were females (61.0%) and 23 were males (39.0%), with mean age of 40.95 ± 14.82 years. Mean age of the H-Pylori positive and negative patients was 42.83 ± 14.5 years and 39.9 ± 15.9 years respectively ($p=0.4$). Total 25(42.3%) patients out of 59 were positive for H-Pylori antigen. Among the total patients, 28 (47.4%) cases were symptomatic and 31 (52.6%) were asymptomatic at the time of presentation. Symptomatic patients had mild mucosal bleeds and none had visceral, intracranial or life threatening bleeds.

Table 1: Comparison of clinical features between Helicobacter pylori positive and negative patients with ITP (n=59)

| Parameters | H pylori positive (n= 25) | H pylori negative (n= 34) | p-value |
|---------------------------|---------------------------|---------------------------|---------|
| Age (years) Mean \pm SD | 42.83 ± 14.5 | 39.9 ± 15.9 | 0.44 |
| Male; n (%) | 9(36) | 14(41) | 0.25 |
| Female; n (%) | 16(64) | 20(59) | 0.25 |
| Asymptomatic; n (%) | 11 (44) | 17 (50) | 0.38 |
| Symptomatic; n (%) | 14 (56) | 17 (50) | 0.38 |
| Dry purpura; n (%) | 8 (32) | 9 (26.5) | 0.31 |
| Wet purpura; n (%) | 6 (24) | 8 (23.5) | 0.21 |

The difference between the age, gender and clinical symptoms of H-Pylori positive and negative group was statistically insignificant (Table 1).

Regarding laboratory results, comparison of platelet count was statistically significant between positive and negative groups (Table-2).

Table 2: Comparison of laboratory results between Helicobacter pylori positive and negative patients with ITP (n=59)

| Parameters | H. Pylori positive patients (n= 25) mean±SD | H. Pylori negative patients (n= 34) mean±SD | p- value |
|--------------------------|---|---|----------|
| Hemoglobin (gm/dl) | 12.21± 1.47 gm/dl | 11.98 ±1.82 | >0.05 |
| Hematocrit (%) | 38.23±1.78 | 37.53±2.37 | >0.05 |
| TLC (10 ⁹ /L) | 8.39 ± 2.86 | 7.63± 2.84 | >0.05 |
| MPV(fL) | 10.80±1.42fl | 9.63±0.95 | >0.05 |
| MCV (fL) | 83.13± 8.74 fl | 86.67 ±8.98 | >0.05 |
| Platelets (µL) | 71.44±18.8 | 57.95±15.1 | 0.03 |

Discussion

Helicobacter Pylori association with immune thrombocytopenia was first time reported by Gasberrini et al from Italy in 1998, in which significant increment in platelet count was observed, after bacterium eradication⁶ Afterwards many studies from Italy and Japan reported the causative role of H-Pylori in ITP and platelet augmentations were seen after eradication therapy.⁷⁻¹⁰ *Helicobacter pylorus* is a gram-negative microaerophilic bacterium that inhabits the human stomach of more than 50% of the world population. H-pylori have evidently been occupied in the pathogenesis of gastric and duodenal ulcers, gastritis and gastric malignancy.¹¹ Numerous studies have proposed that H. pylori infection may be linked with various disorders, comprising pernicious anemia, autoimmune neutropenia, Henoch-Schoenlein purpura, membranous nephropathy, autoimmune thyroid disease and immune thrombocytopenic purpura (ITP).¹² Various studies have shown the link among H-Pylori and ITP. With respect to ITP, role of H-pylori as a causative agent has provided conflicting results. Many reports mainly from Japan show a strong association between the two. Ando K et al reported 83% (50/61) of patients with H-pylori infection in ITP patients.⁷ Some Pakistani studies on ITP have also found a strong association with H-pylori. Shaikh et al reported 63% of H-Pylori infection in chronic ITP patients.¹³ However in American and French population the frequency seems to be low. Michel et al

reported 29% (15/51) positivity of H-Pylori in chronic ITP patients.¹⁴ H-pylori bacterium is easily eradicated and patients with positive H-pylori, ITP may have recovery from thrombocytopenia by the short term eradication therapy.

A local study from Pakistan shows the association, where H-Pylori infection was found high when compared with controls.¹³ This study reported 43.3% prevalence in general control population compared with 63.3% in diseased patients.¹³ Some studies from Turkey, Iran and Korea also favor this association.¹⁴⁻¹⁸ We could not establish a correlation of H-Pylori infection in our ITP patients, as the difference between H Pylori positive and H Pylori negative in chronic ITP patients was statistically insignificant. The association between the two is also not seen in studies from France, Spain and Northern America, where the prevalence in general population is same as in chronic ITP patients^{14, 19, 20}

The mechanism by which H-Pylori can cause thrombocytopenia is unclear but the pathogenetic virulence factors of H pylori such as CagA and VacA are known to play the main role.²¹⁻²³ Several hypotheses have been advanced regarding the mechanisms by which *H-pylori* may cause ITP. One of the mechanism is the molecular mimicry, according to this, *H pylori* could initiate antibody formation secondary to antigens that cross-react against various antigens of platelet glycoprotein.⁵ The important role of CagA-positive H-Pylori strains as a pathogenic bacterium for ITP was recognized in molecular

Table 3: Brief overview of previous studies showing H-Pylori positive ITP patients

| Authors | Total Participants (n) | Male/Female Ratio | Infected persons n(%) | Age (years) of Infected persons (mean±SD) or median(range) | Age (Years) of Non infected persons (mean±SD) or median(range) | Plate Count(µL) of Infected persons | Plate Count (µL) of Non-infected persons (mean±SD) |
|---------------------------------------|------------------------|-------------------|-----------------------|--|--|-------------------------------------|--|
| Gasbarrini et al. (1998) ⁶ | 18 | 5/13 | 11 (61) | 43±14 | 49±12 | 95±39 | 103±24 |
| Jarque et al. (2001) ¹⁹ | 56 | 18/38 | 40 (71) | 54(17-80) | NA | 57±22a | 58±23 |
| Kohda et al. (2002) ²⁷ | 40 | 12/28 | 25 (62) | 54±14 | 48±13 | 67±54 | NA |
| Hino et al. (2003) ⁸ | 30 | 8/22 | 21 (70) | 55±15 | 51±17 | 38±20 | 22±12 |
| Hashino et al. (2003) ³⁰ | 22 | 9/13 | 14 (64) | 53.2±12.9 | 41.8±18.6 | 61±26 | 63±20 |
| Ando et al. (2003) ⁷ | 61 | 12/49 | 50 (82) | 58±11 | 40±16 | 56±24 | 42±24 |
| Michel et al. (2004) ²⁰ | 74 | 21/53 | 16 (22) | 52.5± 15.9 | 38.5±18.3 | 34 (Mean) | 43 (Mean) |
| Takahashi et al. (2004) ²² | 20 | 5/15 | 15(75) | 54±13 | 46±18 | 40±27 | 39±22 |
| Sato et al. (2004) ³² | 53 | 16/37 | 39 (74) | 62 (37-87) | 52 (39-77) | 55 (19-99) | 56 (20-97) |
| Ando et al. (2004) ³¹ | 20 | 5/15 | 17 (85) | 62 (38-83) | NA | 48 (4–86) | 41 (12–82) |
| Nomura et al. (2004) ¹⁰ | 42 | 15/27 | 28 (66) | NA | NA | 29±6 | 31±5 |
| Veneri et al. (2005) ⁹ | 43 | 18/25 | 43 (100) | 52 (28-78) | NA | 54±29 | NA |
| Inaba et al. (2005) ³³ | 35 | 11/24 | 25 (71) | 57 (25-82) | 52±26f | 40 | NA |
| Stasi et al. (2005) ³⁶ | 137 | 57/80 | 64 (47) | 58±13 | 42±16 | 42±25 | 46±23 |
| Fujimura et al. (2005) ³⁸ | 435 | 120/315 | 300 (69) | 59±14 | 47±16 | NA | NA |
| Suzuki et al. (2005) ³⁴ | 36 | NA | 25 (69) | NA | NA | NA | NA |
| Suvajdzic et al. (2006) ³⁵ | 54 | 12/42 | 39 (72) | 54±13 | 42±16 | 68±32 | 78±32 |
| Kodama et al. (2007) ³⁷ | 116 | 32/74 | 67 (58) | 57.9±14.3 | 47.8±17.2 | 39±29 | 30±24 |
| Tag HS, et al (2010) ³⁹ | 25 | 18/7 | 23(92) | 55(35-76) | NA | 78 (6-96) | NA |
| Gan GG,et al (2013) ⁴⁰ | 50 | 12/38 | 11 (22) | 50(19-71) | 49(18-79) | 58 (24-100) | 52(8-97) |
| Hwang JJ et al (2016) ⁴¹ | 102 | 42/62 | 42(41) | 52.9±19.3 | 53.0±11.1 | 43.2±29.1 | 43.1±28.9 |
| Sheema et al, (2017) ⁴² | 85 | 37/62 | 34 (40) | 43.89 ± 7.06 | 44.75 ± 7.91 | 12.3 ± 3.7 | 13.5 ± 4.1 |
| Present study | 59 | 23/36 | 25 (42.3) | 42.8(14.5) | 39.9(15.9) | 71.4 | 57.9 |

studies.⁵ They first reported a decrease in platelet-associated immunoglobulin-G in ITP patients after *H pylori* eradication as well as the existence of a molecular mimicry between the platelet-associated antibodies and the Cag-A protein.⁸ The second study stated that antibodies against Cag-A cross-react with a peptide expressing on platelets of patients with ITP.²³ Although the prevalence of H-Pylori is much higher in developing countries including India, Bangladesh and Pakistan but we are not aware of the strain of bacterium in our population.^{24, 25}

In our patients, no difference in maternal characteristics was seen in H-Pylori positive and negative groups. Findings of many related studies are similar to us but increased prevalence of H-Pylori with increasing age is seen in some of the studies mainly from Japan.^{7, 11, 26, 27} In Japanese population, the *H pylori* was seen significantly in older patients and had more cases of hyperplastic megakaryocytes in the bone marrow compared to those patients without *H pylori* infection.²⁸ An analysis of 20 reported series world-wide showed that 873 ITP patients were H-Pylori positive out of 1367 (64%) (Table-3). The suspicions concerning the definite role of ordinary eradication treatment warranted a study in which 37 known ITP patients of both H-Pylori positive and negative were treated with triple regime therapy, 16 of 26 (62%) patients were responders who were H *pylori* positive, while in the *H pylori* negative patients none was responder.²⁹ The improved platelet count in patients who took PPI single therapy could have been facilitated by a decrease in the amount of *H pylori* and a bacteriostatic influence of the treatment.

Limitations of the study: These include, small sample size and lack of a control group for comparison. Another limitation of our study was inaccessibility of data concerning the bacterium strain identification and eradication therapy. A large sample size would be better indicator of comparison between H pylori positive and negative patients with ITP.

Conclusion

The frequency of H pylori infection in our ITP patients was 42%. The comparative analysis of immune thrombocytopenic patients with H pylori positivity and negativity based on clinico-hematological features

revealed no significant difference in the present study. Future studies with larger sample size and association with eradication therapy will be required to confirm this finding.

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