ORIGINAL ARTICLE

Assessment of the underlying causes of the immune thrombocytopenia: Ten years experience

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Abstract

Objective: Immune thrombocytopenia (ITP) is an immune haematologic disorder causing platelet destruction mediated by anti-platelet antibodies. In this study we aimed to evaluate the clinical and laboratory variables of ITP patients in southeast of Turkey.

Methods: In this retrospective study 167 ITP patients between 2005 and 2015 were evaluated. All patients were screened for immunological parameters including ANA (antinuclear antibodies), anti dsDNA (anti-double-stranded-DNA), ACA(anti-cardiolipin) IgM and IgG, LA (lupus anticoagulants). All patients were screened for Helicobacter pylori, HBsAg (Hepatitis B surface antigen), anti-HCV (hepatitis C virus antibody), and anti-HIV ½ (HIV antibody) and brucellosis.

Results: Among the patients, 50 (29.9%) patients were male, 117 (70.1%) were female. The age range of patients was 18-86 (mean 38.16±14). In 56 patients (33.5%) splenectomy was performed. 36 patients (21.6%) were positive for ANA, 5 (3%) were positive for anti dsDNA, 14 (8.4%) for ACA Ig G, and 14 (8.4%) patients for ACA IgM. LA was tested in 165 patients and 30 (18%) patients were positive for LA. Microbiologic evaluation was as follows: 16 patients (9.6%) were positive for HbsAg, 109 (65.3%) positive for Anti-HBs, 5 positive for anti-HCV (3%), 56 (33.5%) patients were positive for Helicobacter pylori antigen, 5 (2.9%) for Brucella and one patient was positive for anti-HIV ½.

Conclusion: Immune thrombocytopenia patients have to be evaluated according to their demographic characteristics and laboratory results. Secondary causes of ITP were HIV, HCV, Helicobacter pylori, brucellosis, tuberculosis, and autoimmune diseases in our region. Management of ITP patients can change in different regions.

Keywords: Immune thrombocytopenia, Helicobacter pylori, Hepatitis C virus, Brucella, Antiphospholipid antibodies. (JPMA 67: 1004; 2017)

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune haematologic disorder characterized by immune-mediated platelet destruction, impairment of platelet production, and a variable bleeding tendency. ITP is defined as isolated thrombocytopenia with a platelet count < 100 x10^9/L. The classification of ITP depends on the duration of disease based on the following definitions: newly diagnosed (from diagnosis to three months), persistent (3-12 months), and chronic (12 months).[1] Generally, ITP patients with higher platelet counts of > 50 x10^9/L are asymptomatic and frequently diagnosed fortuitously; platelet counts between 20 and 50 x10^9/L are related to excessive bruising with minor trauma; petechiae or ecchymoses develop spontaneously when counts are between 10 and 20 x 10^9/L and spontaneous bleeding may occur. Patients with platelet counts below 10 x 10^9/L are at risk for severe bleeding, such as intracranial haemorrhage or other internal bleeding. The risk of serious bleeding has been conjectural to increase with increasing patient age and among patients with platelet counts persistently < 30 x10^9/L. ITP incidence is approximately 1.6-3.9 per 100.000 person/years in adults.[2-4] Chronic ITP is common in women of childbearing age but the sex incidence is similar in patients over 60.[5] ITP pathogenesis involves a complex network of systemic events including interactions between B and T-lymphocytes and inflammatory cytokines. Autoantibodies against platelet surface glycoproteins, such as GPIIb/IIIa and GPIb/IX complexes, play major roles in both platelet destruction and impaired platelet production. In addition to this, T cell-mediated cytotoxicity may also be involved in its pathogenesis.[6] ITP may be primary or in association with other disorders called secondary ITP. Secondary causes include viral infections such as human immunodeficiency virus (HIV), hepatitis C (HCV), bacterial infections including

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Helicobacter pylori (H. pylori) infections, brucellosis, tuberculosis, certain drugs, and autoimmune diseases including antiphospholipid antibody syndrome, Systemic Lupus Erythematosus (SLE).[7-10] The determination of the demographic features and secondary causes of ITP play an important role on the management of ITP patients. Therefore, in this study we aimed to evaluate the clinical and laboratory variables of ITP patients.

Patients and Methods

In this retrospective study, 167 ITP patients admitted in Dicle University Hospital, Haematology Department, Diyarbakir, Turkey between January 2005 and March 2015 were included. Demographical and haematological data of the patients were recorded. Age, sex, hemoglobin, white blood cells count, platelet count, AST (aspartate aminotransferase), ALT (alanine transaminase), LDH (lactate dehydrogenase) levels were analyzed and evaluated. Definition of bleeding manifestations were based on physical examination. Bleeding signs and symptoms were grouped according to three major domains: skin, visible mucosae and organs. Skin included petechiae, ecchymosis, subcutaneous haematomas, and bleeding from minor wounds. Visible mucosae findings included epistaxis, oral cavity, and subconjunctival haemorrhage.

Organs included gastrointestinal bleeding, haemoptysis, haematuria, menorrhagia, muscle haematoma, haemarthrosis, ocular bleeding and intracranial hemorrhage.

The bleeding was evaluated according to the International Working Group (IWG) bleeding scale (grade 0, grade 1, grade 2, grade 3 and grade 4).[11] The patients were graded based on physical examination at the time of the visit or on patient's history and medical reports. Bleeding manifestations reported by the patient but not visible at the time of data collection were graded 1. Grade 5 was considered to be fatal bleeding.[11]

All patients were screened for immunological paremeters including ANA (antinuclear antibodies), anti dsDNA (anti-double-stranded-DNA), ACA (anti-cardiolipin) IgM and IgG, LA (lupus anticoagulants). ANA were evaluated by immunofluorescence microscopy. Anti-dsDNA, ACA-IgG, and IgM were detected by the enzyme-linked immunosorbent assay (ELISA) method (Abbott GmbH Co & KG, Abbott Laboratories, Chicago, IL, USA). All patients were screened for H pylori by using H. pylori stool antigen test (HpSA (Premier Platinum HpSA; Meridian Diagnostic, Cincinnati, Ohio). HBsAg (Hepatitis B surface antigen), anti-HCV (hepatitis C virus antibody), and anti-HIV ½ (HIV antibody) screening tests were performed by using a fully automated device (Architect, Abbott, IL, USA) with the microparticle enzyme immunoassay (MEIA) method. The blood samples of anti-HIV 1/2 positive donors were confirmed by Western-blot analysis. Diagnosis of brucellosis was performed according to clinical and laboratory findings of the patients: isolation of microorganisms in blood, other body fluids or tissue samples, or the presence of compatible clinical symptoms such as arthralgia, fever, sweating, chills, headache, myalgia, and malaise combined with a serum antibody titer $\geq$1/160 or at least a four-fold increase in this titer by the standard tube agglutination (STA) test in a two or three-week interval. All analyses were performed in accordance with the principles of the Declaration of Helsinki. This study was approved by Dicle University, Faculty of Medicine Institutional Review Board. Descriptive statistics for continuous variables were given as mean, standard deviation, minimum, maximum and median values. Data were analyzed using Statistical Package for the Social Scienses (SPSS) software, version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Among the patients, 50 (29.9%) patients were male, 117 (70.1%) were female. The mean age of patients was 38.16±14 with a range of 18-86 years. The mean number of children of female patients was 3.07±3.12 (range 0-10). According to the IWG bleeding scale, 7% of the patients were assessed in grade 0, 51% in grade 1, 30% grade 2,

Table-1: Immunological parameters of the patients.

Immulogical parameters	Number of the patients
ANA*	36 (21.6%)
ds DNA*	5 (3%)
ACA IgG*	14 (8.4%)
ACA IgM*	10 (6%)
LA*	30 (18%)

*ANA (antinuclear antibodies), anti dsDNA (anti-double-stranded-DNA), ACA IgM (anti-cardiolipin IgM), ACA IgG (anti-cardiolipin IgG), and LA (lupus anticoagulants).

Table-2: Microbiologic evaluation of the patients.

Microbiological parameters	Number of the patients (%)
HbsAg*	16 (9.6%)
Anti HBS*	109 (65.3%)
Anti HCV*	5 (3%)
Anti HIV ½*	1 (0.59%)
H.pylori antigen	56 (33.5%)
Brucella	5 (2.9%)
Mycobacterium tuberculosis	1 (0.59%)

*HBsAg (Hepatitis B surface antigen), anti-HCV (hepatitis C virus antibody), and anti-HIV ½ (HIV antibody).

Table-3: Biochemical laboratory results of the patients.

Biochemical laboratory results	Mean levels
WBC (x10^9/L)*	8
Hb (gm/dl)*	13.12
Platelet count (x10^9/L)	46
LDH (IU)*	220
Total bilirubin (mg/dl)	0.5
AST (IU)*	23
ALT (IU)*	25

*WBC (white blood cell), Hb (hemoglobin), LDH (lactate dehydrogenase), AST (aspartate aminotransferase), ALT (alanine transaminase).

10% were in grade 3 and 2% in grade 4. Out of the patients 68% were from rural area. A total of 48 (28.7%) patients were smokers. In 56 patients (33.5%) splenectomy had been performed. Thirty six patients (21.6%) were positive for ANA, 5 (3%) patients were positive for dsDNA, 14 (8.4%) for ACA IgG, 14 (8.4%) patients for ACA IgM. Lupus Anticoagulant was tested in 165 patients and 30 (18%) patients were positive for LA (Table-1). Microbiologic evaluation was as follows: 16 patients (9.6%) were positive for HbsAg, 109 (65.3%) positive for anti-HBs, 5 positive for anti-HCV (3%), 56 (33.5%) patients were positive for Helicobacter pylori antigen, 5 (2.9%) for Brucellosis and one patient was positive for anti-HIV ½ (Table-2). One patient was diagnosed as splenic tuberculosis. Mean laboratory levels results were as follow: white blood cell counts 8 x10^9/L, haemoglobin 13.12 gm/dl, platelet counts 46 x10^9/L, LDH 220 IU, total bilurubin 0.5 mg/dl, ALT 25 IU, AST 23 IU (Table-3). APS developed in three patients (2 female, 1 male). We did not detect a significant difference between smokers and non smokers in platelet numbers and grade of bleeding ($p>0.05$).

Discussion

ITP is an acquired immune disorder characterized by thrombocytopenia and mucocutaneous bleeding and it is commonly assumed that ITP results from autoantibodies causing accelerated platelet destruction. Autoantibodies may also inhibit platelet production.[6] ITP is more common in women than in men between the ages of 30 and 60 years.[5] In a Pakistani study with 86 chronic ITP patients, 64% of the patients were female, with a mean age at the time of diagnosis of 25.5 years (range: 2-65 years).[12] Elezovic et al. reported that 136 out of 167 patients with chronic ITP were women (81.4%) and median age of their patients was 35 years.[13] In an Irani study on 90 patients with chronic ITP, mean±SD age at diagnosis was 36.7±14.2 years and 77.8% were women.[14] In a recent study of Payandeh et all. on patients with acute ITP, the mean±SD age of the patients was 39.1±13.3 years and 62.3% were women.[15] In our study median age was 38 years and the big majority of the patients were female, similar to other studies. The females are generally more frequently affected than males for many autoimmune diseases. The studies suggested that gender differences were related to the T cell and antibody responses that occur in autoimmune diseases. Females have increased immune reactivity, differences in the number or responsiveness of cells that constitute the immune response. Hormonal changes during pubertal maturation, pregnancy, and menopause may alter susceptibility to autoimmunity. Genetic factors and differential exposure to environmental factors including sunlight, can influence the prevalence of an autoimmune disease.[16] In spite of these data, further studies are needed for determination of relationship between sex and ITP.

Smoking can cause significant increase in the platelet aggregability in ITP patients. The increase in platelet aggregability can be explained on the basis of increased platelet aggregating agents such as epinephrine and nor-epinephrine and injury to the endothelium or direct effect on platelets. Some studies reported that an increase in the epinephrine levels could cause release of platelets in circulation. However, in many studies, no significant change was found in the platelet counts in smokers.[17] In our study 28,7% of the patients were smokers and we did not detect a significant difference between smokers and non smokers in platelet numbers and the grade of bleeding. We concluded that clinical findings including large scale studies were necessary on platelet numbers and platelet activity with bleeding risk.

Bleeding manifestations in patients with ITP range from mild skin bruises to life-threatening intracranial haemorrhage. Severe bleeding occurs when the platelet count falls $<10 \times 10^9$/L.[18] In our study according to the International Working Group (IWG) bleeding scale, 7% of the patients were assessed in grade 0, 51% in grade 1, 30% grade 2, 10% were in grade 3 and 2% in grade 4 and bleeding manifestations were similar to the literature data.[18]

Helicobacter pylori is a common pathogenic bacterium in the stomach that infects almost half of the population worldwide. Helicobacter pylori was implicated in the pathogenesis of extra-digestive disorders, including cardiovascular, haematologic, and autoimmune diseases such as ITP. Various studies showed that ITP improved after H. pylori eradication.[19-21] The prevalence of H. pylori infection is 70% in Japanese ITP patients, 22% in North American chronic ITP patients, 29% in patients with ITP of

white French origin.[20] The prevalence of H. pylori was reported to be 27.8% in Iran, 63.3% in Pakistan in chronic ITP patients.[14,21] In presented study H. pylori prevalence was 33.5% in ITP patients. On the other hand H. pylori infection is usually acquired in early childhood and in our country H. pylori prevalence was higher (>80%) in general population.[22] We suggested that the group of ITP patients with symptoms or those from highly endemic regions should be considered for H. pylor) detection testing and therapy.

Many haematological abnormalities, such as pancytopenia, anaemia, and leukocytosis, can be associated with tuberculosis (TB). However ITP is an extremely rare event in TB. In Turkey ITP was reported in a 46-year-old male patient with pulmonary tuberculosis.[23] We also presented a female case with 58-year-old with splenic tuberculosis and ITP in Diyarbakir.[24] We thought that in the endemic regions for TB, tuberculosis should be considered as a secondary reason of ITP.

The pathogenetic role and the clinical importance of the presence of antiphospholipid antibodies (APAs) in patients with immune ITP are not clear. In a Turkey study the prevalence and clinical significance of APAs were investigated in patients with ITP. Eighty-two newly diagnosed ITP patients were prospectively studied. Thirty-one patients (37.8%) were APA positive at diagnosis. In addition, LA was an important risk marker for the development of thrombosis in ITP patients. After a median follow-up of 38 months, 14 ITP patients (45%) who had APA positivity developed clinical features (thrombosis or foetal losses) of antiphospholipid syndrome (APS). The positivity rate for LA was significantly higher in those patients with ITP who developed APS.[25] In our study 14 (8.4%) patients for ACA IgM, 10 (6%) patients for ACA IgG. Lupus Anticoagulant was tested in 165 patients and 30 (18%) patients were positive for LA. In our study APS developed in three patients. According to the data we suggested that in patients with ITP, the persistent presence of APAs was an important risk factor for the development of APS.

Hepatitis C virus has been reported to be associated with the occurrence of autoimmune disorders, including ITP. A study with 150 subjects reported that the prevalence of severe thrombocytopenia was significantly higher in ITP patients compared with that in chronic HCV patients.[26] In our study 3% of the patients were HCV positive and we suggested that ITP patients should be screened for HCV antibody.

Brucellosis constitutes a major health problem in many parts of the world, particularly in the Mediterranean and the Middle East. Severe thrombocytopenia is a rare haematologic manifestation of brucellosis. Prompt recognition of this brucellosis complication and aggressive therapy is vital because the mortality rate associated with bleeding into the central nervous system is high. Altuntas et al. reported a case of brucellosis who was admitted with a severe thrombocytopenic purpura. The patient responded well to intravenous gamma globulin (IVIg) treatment with platelet recovery within 2-3 days.[27] In cases of brucella induced immune thrombocytopenia, corticosteroid treatment might be useful for the prevention of bleeding complications.[28,29]

Thrombocytopenia is a common feature among HIV positive patients. However, there are few reports about this subject after highly active antiretroviral therapy (HAART). In a trial conducted in 55 HIV positive outpatients with thrombocytopenia in Brazil, in 63.6% patients, the cause of thrombocytopenia was classified as ITP and non immune in 25.5%.[30] Various studies indicated that about 5% to 10% of HIV infected patients develop thrombocytopenia during the course of the disease, and ITP may be the sole clinical manifestation of HIV infection. Steroids, IVIGs, and antiretroviral therapy (ART) have all been tried with varied results but have been associated with fall in platelet count on withdrawal of therapy. Shah I. et al. reported a case of a 13-year-old girl who presented with thrombocytopenic purpura and had no response to ART but had normalization of platelet count while on steroids, which immediately fell below the normal range on withdrawing the steroids.[31] In our study we detected anti HIV ½ positivity in one patient. Our result and literature data presented that thrombocytopenia remained a problem among HIV patients and a diagnostic approach related to the haematological consequences of HIV infection is needed for a better therapy option for this population.

In conclusion ITP was more common in females than in males. Gender differences may be related to the T cell and antibody responses, increased immune reactivity, differences in the number or responsiveness of cells that constitute the immune response, hormonal changes during pubertal maturation, pregnancy, and menopause. In our study we did not detect a significant difference between smokers and non smokers in platelet numbers. In presented study H. pylori prevalence was 33.5% in ITP patients. H. pylori should be detected and eradicated in ITP patients. HIV, HCV, brucellosis, tuberculosis, and autoimmune diseases including APS and SLE may be the other secondary cause of ITP so detection and treatment of secondary causes of ITP may contribute to the management of ITP patients.

Disclaimer: None.

Conflict of Interest: All authors declare that there is no conflict of interest or financial support.

Funding Sources: None.

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