Original Article

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A Study of Epidemiology and Therapeutic Response of Patients with Immune Thrombocytopenic Purpura

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Abstract

Background: Immune thrombocytopenic purpura (ITP) is a disease characterized by decrease of the peripheral blood platelet count. The disease presents in acute and chronic forms. Because of the importance and high prevalence of ITP, it was decided to study the therapeutic response of patients with ITP.

Material and Methods: A cross-sectional study was conducted at Ghaem hospital, Mashhad, Iran. The diagnosis was based on clinical symptoms and laboratory findings. All of the patients were treated by ITP conventional treatment. Then, the therapeutic response was evaluated.

Results: The population of this study included 288 ITP patients, 159 were diagnosed with acute ITP (132 pediatric: 6 months to12 years and 27 adult: 13-58 years old) and 69 with chronic ITP (43 female and 26 male). Among pediatric patients, 75 were girls and 57 boys. The mean age in acute ITP was 11 years and in chronic ITP was 28 years old. According to T-test, significant relation was found between age in type of ITP (P=0.000). In men, %77 suffered from acute ITP and %23 from chronic form while in female acute ITP was %62 and chronic ITP was %38. According to Fisher-Test, no significant relation was found between sex in type of ITP (P=0.842). After the conventional treatment with prednisolone, 19 cases were considered as corticosteroid-refractory ITP. The second step in treatment of corticosteroid-refractory ITP was splenectomy. Responsiveness to splenectomy was 84% and 16% were unresponsive to splenectomy and immunosuppressive therapy, and they expired with signs of bleeding.

Conclusion: The acute type of ITP was common among patients at age range of 3 to 4 years. The chronic ITP was more common among adults and also more frequent in female. Splenectomy in patients with chronic ITP was associated with a good response in most cases, but the response to immunosuppressive agents in this group was poor.

Keywords: Epidemiology, Response, Platelet, Purpura, Thrombocytopenia

Introduction

Immune thrombocytopenic purpura (ITP) is one of the most important and frequently encountered forms of enhanced consumption of platelets and an unpredictable syndrome in its clinical course that affects both children and adults. ITP can be recognized by isolated bleeding symptoms without constitutional symptoms (e.g. significant weight loss, bone pain, night sweats) and the absence of hepatosplenomegaly, lymphadenopathy or stigmata of congenital conditions. The hallmark of ITP is isolated thrombocytopenia (platelet count <100 x 10 9/L) ; anemia only if due to significant bleeding -- otherwise normal red cell indices , white blood count and differential identified platelets should be normal to large in size. Anemia and/or neutropenia may indicate other diseases.

Increased level of anti-platelet antibody in serum, destruction of platelets, and naturalization or increase of megakaryocytes in bone marrow (1-5).It is the most common cause of thrombocytopenia without anemia or neutropenia. It is usually idiopathic but may be seen in association with other

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diseases such as systemic lupus erythematous (SLE), human immunodeficiency virus (HIV) infection, viral hepatitis, Helicobacter pylori infection, chronic lymphocytic leukemia (CLL), and Hodgkin lymphoma or autoimmune hemolytic anemia (6-8). It is believed that the reduction in platelet count is due to their rapid clearance via reticuloendothelial system, which subsequently increases the capacity of bone marrow to produce platelets (1, 9-11). Many patients have no clinical problems, but depending upon the severity of thrombocytopenia, the risk of bleeding increases. ITP was considered as an autoimmune disorder wherein the autoantibodies attach to platelets and the opsonized platelets removed prematurely via Fcγ receptors of macrophages in the reticuloendothelial system, especially in the spleen. The normal lifespan of a platelet is 10 days but in ITP this is reduced to a few hours (6, 12). These autoantibodies are generally IgG and accelerate destruction of platelets, resulting in thrombocytopenia and may also impair megakaryocyte growth and platelet release. Measurement of antiplatelet antibodies level remained unreliable and autoantibodies are not detectable in up to 50% of patients so the diagnosis is made by demonstrating isolated thrombocytopenia without an obvious cause (8,13,14).T-cells also play a role in ITP pathogenesis. Anti-platelet antibodies are generated by expansion of B-cell clones, but these are generated under the control of T helper cells and inflammatory cytokines. Children and adults with chronic ITP show an increased level of serum inflammatory cytokinases, such as interleukin-2, interferon-γ, and IL-10. (14)

The disease can be manifested as either acute or chronic type that differ in incidence, prognosis, and therapy (8, 15). Acute ITP, defined as thrombocytopenia occurring for <6 months and usually resolve spontaneously. Chronic ITP last more than 6 months, requires therapy to improve the thrombocytopenia. The ratio of incidence in females to males is nearly 1:1 in acute ITP while is 2 to 3:1 in chronic ITP (16). In most children, ITP is an acute, self-limited disease that may follow a viral illness or immunization. Thrombocytopenia may be presented with extensive petechie, purpura, bruises, and bleeding from mucous membranes. In many adults, ITP is heterogeneous and may be chronic and poorly responsive to treatment. Most thrombocytopenic patients suffering from clinical problems related to their thrombocytopenia experience only epistaxis, petechie, and bruising, while others have major rare bleeding from the outset such as intracranial hemorrhage, protracted epistaxis, hematuria, hemoptysis, and gastrointestinal bleeding (7,13).

The platelet count is usually 10–100 × 109/L. The haemoglobin concentration and white cell count are typically normal unless when there is an iron deficiency anemia because of blood loss. Some patients may show neutrophilia or lymphocytosis due to a concomitant or recent viral or bacterial infection. Then, experienced eyes should examine the blood smear. Findings inconsistent with the diagnosis of ITP are giant platelets, schistocytes, macrocytes, and nucleated red blood cells or similarly. Bone marrow aspiration is not necessary in children with a typical clinical presentation of ITP if there is any hepatomegaly, splenomegaly, lymphadenopathy or any clinical or laboratory feature suggesting the presence of another disease, a bone marrow examination should be performed (7). Clinically, patients with refractory ITP pose a major challenge since, by definition, they are resistant to many of the treatments in current use. They often have low platelet counts, in addition to bleeding that is difficult to control since the disease is unresponsive to conventional therapies (7, 8).

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The standard initial treatment for ITP, especially in chronic type, is corticosteroid therapy (1, 5, 17, and 18) that is widely used for the treatment of ITP for several decades. Splenectomy is the appropriate next step for most adults who have a relapse or have not had a response to corticosteroids, intravenous immune globulin, or anti-D immune globulin (8).This surgery therapy results in removal of the major site of anti-platelet antibody synthesis and antibody-coated platelets destruction (19). Children undergoing splenectomy should receive Hemophilus influenza type b vaccine and conjugate Pneumococcal vaccine (8, 18). Because the protection provided by vaccines is incomplete, daily prophylaxis with penicillin is recommended for the patients up to five years of age and for at least one year after splenectomy (8). The long-term effects of splenectomy in ITP remained still unknown. For the 20%-25% of patients that do not respond to the therapeutic procedure and remain profoundly thrombocytopenic, many therapeutic alternatives have been used (20).

The aim of this study was first to investigate the relation between type of ITP and age along with sex. Secondly, this study attempted to evaluate the treatments in ITP and the responses to these treatment.

Materials and Methods

A cross-sectional study was performed on 228 patients with ITP in the age range of 1 to 58 years attending Ghaem hospital, Mashhad University of Medical Sciences, Iran, from May 2008 until April 2013. The diagnosis was based on clinical symptoms and laboratory findings. All of the patients had at least one type of mucocutaneous bleedings, without spelnomegaly and hepatomegaly. For all the patients CBC (cell blood count) and peripheral blood smear were performed. The peripheral blood platelet count was 10-100×109/L. White blood cell count and differential were normal. Red blood cell, Hemoglobin (Hb), Hematocrit (Hct) was normal. All adult patients were newly diagnosed with ITP tested for HIV and HCV. Anti-nuclear antibodies, platelet parameters obtained on automated analyzers in the evaluation of patients with suspected ITP. The patients with peripheral blood platelet count more than 100000/mm³, abnormal white blood count, abnormal differential and blast in peripheral blood, splenomegaly, hepatomegaly. History of coagulation disorders, history of platelet dysfunction disorder, and history of hemolytic anemia were excluded from the study.

A numerous of acute ITP had recovery without treatment and others were treated by ITP conventional treatment. The consumption dose of corticosteroid was 1 to 1.5 mg/ kg for at least 6 weeks.

Corticosteroid-therapy was prescribed for 96 patients (69 patients with chronic type and 27 with acute who were transformed to chronic type). The cases who had several periods of remission and relapse, or who needed high-dose steroid therapy to maintain an appropriate platelet count were considered as corticosteroid-refractory ITP (%19.8). In corticosteroid-refractory ITP, splenectomy was done and then response to treatment was checked out (%84). For cases that were resistant to spelenectomy, immunosuppressive therapy was performed.

Then, collected data was analyzed by SPSS Version 20.0 and Minitab software.

Results

This study was performed on 228 patients with ITP,114 cases were male and 114 were female (1:1 male-to-female ratio) in the age range of 1 to 58 years. The mean age was 18.59.±14.64 and the minimum age was 6 month and the maximum age was 58 years (Figure 1). The mean age in male was 17.70±15.94 and in female 19.38±13.43. According to T-test, no significant relation was found between males and females considering age (P=0.486) (Figure 2).

Among 228 ITP patients, 159 subjects had signs of the acute type. Among these

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cases, 132 were children (Figure3) including 75 boys and 57 girls (Figure 4), and 27 were adults with acute signs. The total number of patients with chronic type was 69 (43 women and 26 men) (Figure 3).

In the men, %77 were acute form of the disease and %23 were chronic form while in female acute ITP was %62 and chronic ITP was %38. According to Fisher-test, no significant relation was found between sex and type of ITP (P=0.842) (Figure 5).

The total number of patients with chronic type was 69 (43 women and 26 men). Corticosteroid-therapy was prescribed for 96 patients (69 patients with chronic type and 27 acute type who were transformed to chronic type). Among these patients, 19 cases indicated corticosteroid- refractory ITP, so they were subjected to splenectomy.

According to these criteria, 19 patients were included in this category, and thus splenectomy was performed with patient's consent. The response to splenectomy was very good in 16 patients (84%), so that the clinical manifestations and laboratory findings disappeared and the platelet count increased. In 3 patients (16%) who were splenectomy-resistant and their clinical bleeding symptoms had still remained, immunosuppressive agents were prescribed, but no response was observed (Table I).

Table I. The results of treatment of 96 patients with acute ITP

Treatment Modality	NO.	Response to treatment (%)	Mortality
Corticosteroid therapy	96	77(80.2)	-
Splenectomy	19	16(84%)	-
Immunosuppression	3	-	3

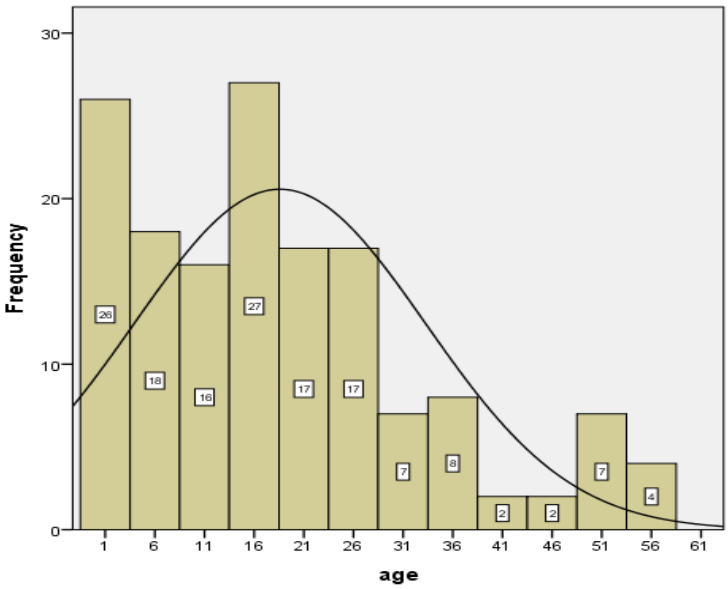

Figure 1. Frequency of age in patient with ITP

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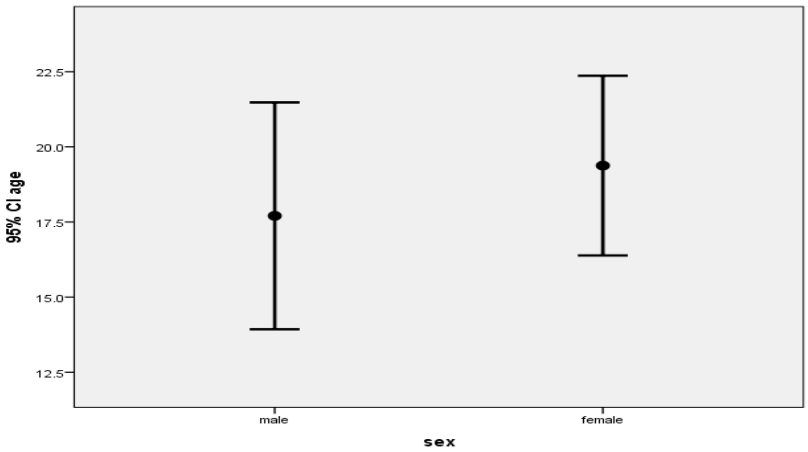

Figure 2. Average age according to sex (Error Bar Accordigto the confidence interval

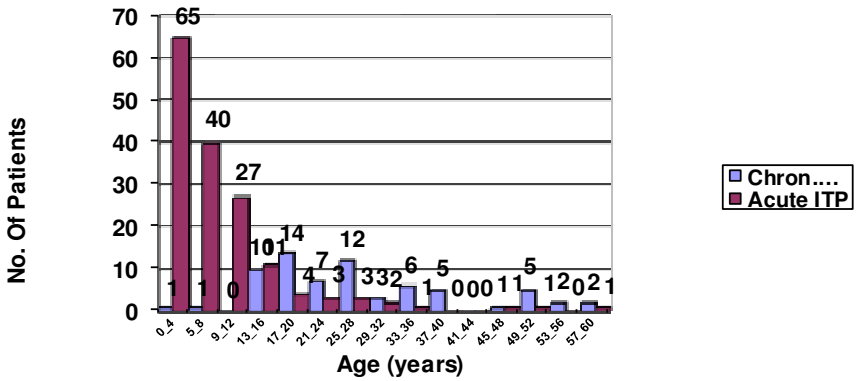

Figure 3. The prevalence of acute and chronic ITP

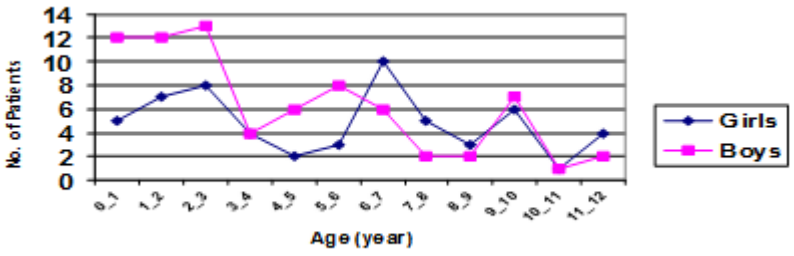

Figure 4. The prevalence of acute ITP in children

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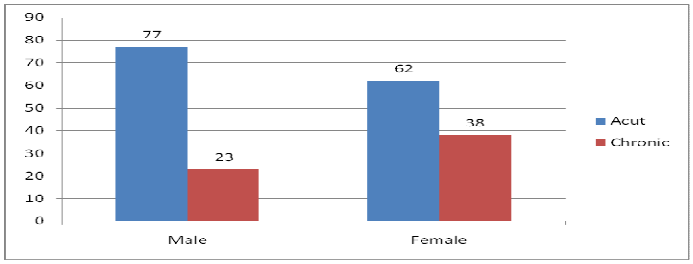

Figure 5. Frequency of sex according to the type of ITP

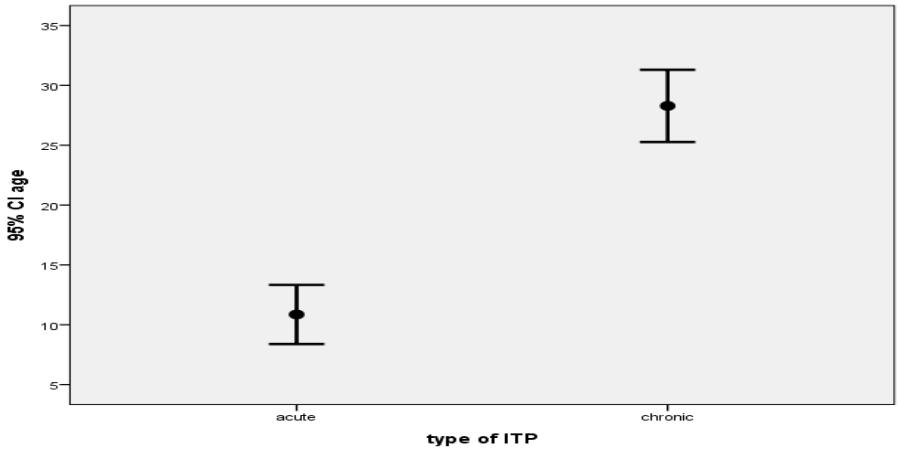

Figure 6. The mean age of patients with acute and chronic ITP (Error bar according to Confidence Intervalt)

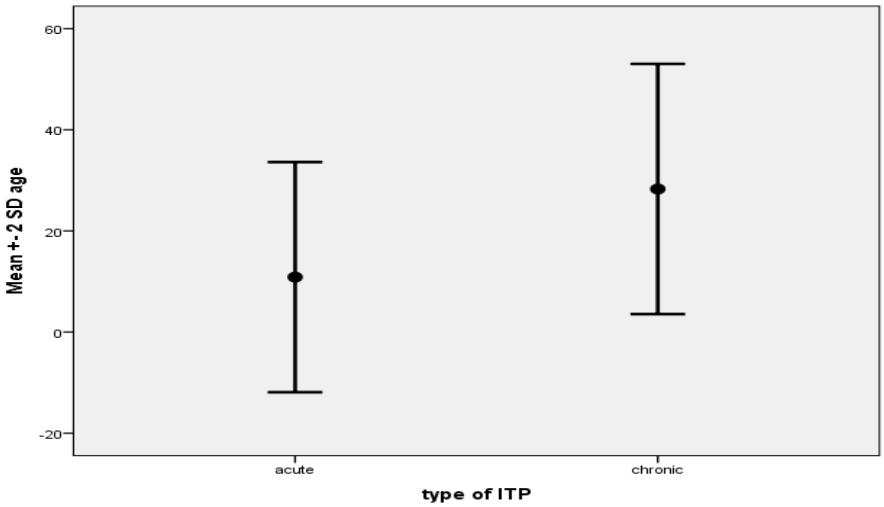

Figure 7. The mean age of patients with acute and chronic ITP (Error bar according to standard deviation)

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Discussion

ITP is a disease that is associated with shortening lifespan and accelerated destruction of platelets by reticuloendothelial system, particularly by the spleen. Nowadays, it has been clearly known that this disease is an immune-mediated disorder (1, 18-20). ITP can be classified as acute or chronic type. The acute form is most common in children aged between 2 to 6 years with no difference between two sexes. Acute ITP usually has a very sudden onset. Although spontaneous recovery occurs in 80-90% of patients within 4 months of diagnosis, hemorrhagic complications may occur (21). In this study, 228 patients with ITP were chosen who referred to Ghaem Hospita, 114 cases were male and 114 cases were female (male-to-female ratio = 1:1), of which 159 patients were diagnosed with acute form. Among these patients, 132 were children (male-to-female ratio =1:1.3), and 27 patients were adults. Therefore, the acute type of ITP was mostly observed among people younger than the puberty, and the maximum age was 3 to 4 years old (Figure 3). Chronic type was diagnosed in 69 patients (43 women + 26 men). The female to male ratio was 1.65 to 1, so it can be concluded that the chronic ITP was more prevalent in women than in men.

The mean age of patients with acute ITP was 10.68±11.38 and the mean age in patients with chronic ITP was 28.28±12.36. According to T-Test, significant relation was found between age and type of ITP (P = 0.000) (Figure 6, 7)

In a study in Iran in 2014, Sajedeh Saeidi evaluated 323 patients with ITP. The patients were classified based on the age into childhood ITP (3 months to 16 years of age) and adult ITP (16≤ years) groups. Among the thrombocytopenia patients, 223 patients (69%) had childhood ITP with a mean age of 3.6 years, and 100 patients (31%) had adult ITP with a mean age of 34.3 years. The prevalence of disease in females and males under the age of 16 and older was 57.1% (n=93), 81.2% (n=130), 42.9% (n=70), and 18.8% (n=30), respectively. The overall prevalence was 49.5% (n=160) in males and 50.5% (n=163) in females. Childhood ITP was more frequent in males than females, while the ratio of females was higher in adult ITP and the whole number of patients (P=0. 0001). Sixty six patients were infants (3 months to 1 year of age), among whom 43 (65.2%) were male and 23 (34.8%) were female (22). Doan et al., concluded that females are typical adults with ITP, generally occurring between 18 to 40 years of age (23).

Henrik Frederiksen and Kai Schmidt searched 221 adult ITP patients. Considering sex, 139 were women (63%) and 82 men (37%), yielding a female to male (F/M) ratio of 1.7:1 The median age of the entire population was 56.4 years (females, 55.6 years; males, 61.6 years). In patients older than 60 years, the F/M ratio was 1.3; in patients younger than 60 years, the F/M ratio was 2.1. This difference was not significant (24).Corticosteroid-therapy was prescribed for 96 patients (69 patients with chronic type and 27 subjects of acute form who were transformed to chronic type. Among these patients, 19 cases indicated corticosteroid- refractory ITP, so they were subjected to splenectomy. Although 16 patients showed a good response to splenectomy, 3 cases of corticosteroid-refractory ITP were unresponsive and despite the administration of immunosuppressive agents, they did not even respond to this treatment and passed away.

Dameshek, and Rubio used prednisone for the treatment of 30 consecutive patients with ITP. Eleven cases were diagnosed with acute and 19 cases with chronic type. The initial dose of prednisone varied between 20 and 150 mg. per day, which was taken orally. Twenty two out of 30 cases the platelet count rose from the initial low values to normal in 6 to 150 days. Much individual adjustment of

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dosage was necessary. Maintenance dosages ranged from 2.5 to 15 mg. per day, but in eight patients it was possible to withdraw the prednisone entirely after establishing a normal platelet count. Splenectomy was performed in five patients of this series but was followed by complete, sustained remission in only one case. It can be concluded that in the treatment of ITP chief reliance should be placed upon such measures as prednisone therapy and transfusions, splenectomy being reserved for the occasional severe cases that did not respond to medical measures (25).

Although many advances have been achieved in the understanding of ITP, critical issues regarding the pathophysiology and biology of the disease remain to be elucidated. The recent characterization of the human genome along with new sophisticated molecular biology techniques will allow basic researchers to study genes that may affect the presentation and clinical course of the disease. Different patterns of gene expression in this population can be studied, leading to the identification of subsets of patients with ITP at higher risk of bleeding. A pattern of multigene expression might also provide clues about regulatory mechanisms and broader cellular functions (20).

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