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Prevalence, Prognosis, and Outcome in Egyptian Children with Primary Immune Thrombocytopenia: A Single-Center Experience

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ABSTRACT

Background: Idiopathic (immune) thrombocytopenic purpura (ITP) is a heterogeneous clinical disorder characterized by immune-mediated platelet destruction. ITP is usually a benign, self-limiting disease in children.

Objective: To assess prevalence, prognosis, and outcome of Egyptian children with primary immune thrombocytopenia.

Patients and Methods: This cross-sectional study was carried on 80 children (1-13 years) with primary ITP who presented to the Pediatric Hematology Unit and outpatient clinic of Zagazig University Hospitals, during the period from April 2020 to June 2021. Patients were divided into two groups; Group (1): included 20 healthy matched subjects (control), Group (2): included 60 patients with primary ITP. The group was subdivided into 3 subgroups, Subgroup (2A) included 20 patients with newly diagnosed ITP, Subgroup (2B) included 20 patients with persistent ITP, and Subgroup (2C) included 20 patients with chronic ITP.

Results: There were significant differences between the studied groups in age, sex, and weight. There was a statistically significant association between prognosis and general characteristics of the studied ITP patients.

Conclusion: primary ITP in children is a nonthreatening and self-limited disease, usually lasting less than one year, and chronic form has different prognostic parameters. The use of these parameters can early distinguish children who are expected to have short and uneventful disease duration, to minimize their exposure to pharmaceutical intervention.

Keywords: Immune thrombocytopenic purpura, Cytokines, Thrombopoietin, Reticulated platelets.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder characterized by an isolated low platelet count in which platelets are destroyed mainly in the reticuloendothelial system. The disorder is defined as primary ITP in the absence of other causes or disorders that may be associated with thrombocytopenia [(1)].

The pathogenesis of ITP is relatively complicated, the definite pathogenesis and cause remain unclear up to the present. More recent evidence suggests that multiple mechanisms contribute to thrombocytopenia in ITP patients. Increasing studies have found that T-cell subsets, regulatory B cells (Bregs), dendritic cells, myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells are all involved in the pathogenesis of ITP[(2)].

The true incidence of ITP is unknown, as those with a more mild form of the disease may never come to medical attention. However, there are published data on the reported incidence and prevalence of ITP in different parts of the world without substantial differences [(3)].

ITP presents as a primary form characterized by isolated thrombocytopenia (platelet count < 100×10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia, or a secondary form in which immune thrombocytopenia develops in association with another disorder that is usually immune or infectious [(4)].

According to the standardization of terminology, definitions and outcome criteria in ITP in children is divided into newly diagnosed (duration < 3 months, 50% of the cases), persistent (3–12 months, 25% of the cases), and chronic (>12 months, 25% of the cases) type. The older time limit of 6 months to define chronicity is no longer in use [(5)].

Immune thrombocytopenia (ITP) in children is a disorder with a favorable prognosis characterized by increased platelet destruction and decreased platelet number. It may be triggered by viral infection or immunization[(1)]. Newly diagnosed ITP in children is usually a short self-limiting disorder without any late sequelae; in most cases, ITP lasts for several weeks or months, although in 5% to 30% of affected children, the condition becomes chronic. Chronic ITP (cITP) is associated with a high risk of bleeding, such as cerebral hemorrhage, and often requires the restriction of physical activities [(6)].

This study aimed to assess the prevalence, prognosis, and outcome of Egyptian children with primary immune thrombocytopenia.

PATIENTS AND METHODS

This cross-sectional study was carried on 80 children (1- 13 years) with primary ITP who presented to the Pediatric Department, Zagazig University Hospitals, during the period from April 2020 to June 2021.

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The study included 80 patients diagnosed with 1ry ITP, all patients were subjected to CBC, and bone marrow.

Ethical Considerations:

Written informed consent was obtained from all children's parents and the study was approved by the research ethics committee of the Faculty of Medicine, Zagazig University (international review board ZU-IRB #). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

ITP was diagnosed based on history, physical examination, and laboratory results including (1) isolated thrombocytopenia (platelet count 100×10^9 /L), normal hemoglobin concentration, and normal white blood cell count; (2) normal peripheral blood smear finding except for the presence of giant platelets and thrombocytopenia.

Inclusion criteria: Children ages between 1 and 13 years, both sexes, and patients with primary ITP.

Exclusion criteria: Patients under 1 year or above 13 years, patients with secondary immune thrombocytopenia, active infection at the time of diagnosis, therapy or drugs causing thrombocytopenia, and splenomegaly; any definitive conditions or diseases resulting in thrombocytopenia.

All patients will be subjected to the following measures:

1- A detailed history about the onset of the disease, bleeding manifestations, course of the disease, recent viral infection, and exclusion of any cause of secondary ITP such as SLE.
2- Physical examination includes anthropometric measures: weight in kg, height in cm, lymph nodes and abdominal organs examination
3- Thorough clinical examination with special emphasis on clinical signs of bleeding such as bruising or purplish areas on the skin, mucous membranes or gums, menorrhagia, blood in urine or stool, and any associated splenomegaly.
4- Laboratory investigation: (a) Complete blood count (CBC) was done (at the start and after 3 months) on LH750 Beckman Coulter-Miami, Florida, USA, and Leishman stained peripheral blood smear. (b) Bone marrow examination by direct puncture of ASIS obtaining both bone marrow slide smears and bone marrow samples on EDTA vacutainer tubes.

A bone marrow aspirate was performed to exclude other diseases resulting in thrombocytopenia.

Follow up: at least one year

All patients were followed up for at least one year to assess the outcome and prognosis.

Statistical analysis:

Statistical analysis was done using SPSS software version 27 (IBM, 2020). Data were presented in tables and figures. Quantitative data were presented as mean, median, standard deviation, and range. Qualitative data were presented as frequencies and proportions. Shapiro–Wilk test was used to determine the distribution characteristics of variables and variance homogeneity. The Chi-square test ($\chi 2$) was used to test differences for categorical variables. Mann-Whitney U test (MW) was used to test differences for continuous variables between two groups. One-way ANOVA test (F) was used to test differences when more than two independent groups were present and variances were equal, while the Kruskal-Wallis test (KW) was used when equal variances were not present. P-value < 0.05 was considered significant.

RESULTS

Table (1): General characteristics of the studied groups

Variables	Newly diagnosed ITP (n=20)	Persistent ITP (n=20)	Chronic ITP (n=20)	Control group (n=20)	P-value
Age (years): Mean ± SD Median	 5.2 ± 4.4 3.0	 6.1 ± 3.4 7.0	 9.6 ± 4.2 10.0	 6.1 ± 4.2 5.0	 **0.03** **S**
Sex: Male Female	 9 (45%) 11 (55.5%)	 8 (40.0%) 12 (60.0%)	 17 (85%) 3 (15%)	 9 (45%) 11 (55.5%)	 **0.04** **S**
Weight (Kg): Mean ± SD Median	 18.4 ± 9.5 15.0	 22.3 ± 8.6 25.5	 35.0 ± 18.6 33.0	 21.2 ± 12.0 16.5	 **0.02** **S**
Consanguinity: Positive Negative	 4 (20.0%) 16 (80.0%)	 4 (20.0%) 16 (80.0%)	 7 (35%) 13 (65%)	 5 (25%) 15 (75%)	 0.8
Age at diagnosis (years): Mean ± SD Median	 5.2 ± 4.4 3.0	 5.4 ± 3.4 6.0	 4.6 ± 2.7 5.0	-	 0.8
subcutaneous bleeding: Yes No	 20 (100%) 0 (0.0%)	 17 (85%) 3 (15%)	 17 (85%) 3 (15%)	-	 0.3
Bleeding per orifice: Yes No	 11 (55%) 9 (45%)	 16 (80.0%) 4 (20.0%)	 15 (75%) 5 (25%)	-	 0.3
Initial Platelets count: Mean ± SD Median	 8.3 ± 5.7 9.0	 16.9 ± 17.3 6.0	 21.4 ± 15.6 18.0	-	 0.1
Initial blood hemoglobin: Mean ± SD	 10.4 ± 1.1	 10.9 ± 1.9	 10.9 ± 1.6	-	 0.6
Follow up Platelets count: Mean ± SD Median	 247.7 ± 41.6 320.0	 101.4 ± 8.4 65.0	 143.0 ± 16.1 130.0	-	 **0.01** **S**

Table (1) showed that there were statistically significant differences between the studied groups in age, sex, and weight. Chronic ITP patients had higher age, higher weight, and more males. There were statistically significant differences between the studied patients in follow-up Platelets count. Newly diagnosed ITP patients had the highest follow-up Platelets count followed by chronic ITP patients.

Table (2): Bone marrow examination of the studied ITP patients

	Newly diagnosed ITP (n=20)	Persistent ITP (n=20)	Chronic ITP (n=20)	χ^2	P-value
Hyper-cellular megakaryocyte	14 (70%)	20 (100%)	16 (80.0%)	5.7	0.2
Normal	2 (10%)	0 (0.0%)	0 (0.0%)		
Not done	4 (20.0%)	0 (0.0%)	4 (20.0%)		

Table (2) showed that there was no statistically significant difference between the studied ITP patients in bone marrow examination.

Table (3): Received treatment in the studied ITP patients

	Newly diagnosed ITP (n=20)	Persistent ITP (n=20)	Chronic ITP (n=20)	χ^2	P-value
Non-specific treatment	3 (15%)	0 (0.0%)	0 (0.0%)	4.2	0.1
Corticosteroid	13(65%)	17 (85%)	13(65%)	2.0	0.3
IVIG	13 (65%)	20 (100%)	11 (55%)	8.9	**0.01(S)**
TPO oral	0 (0.0%)	7 (35%)	13(65%)	11.3	**0.002(S)**
TPO SC	0 (0.0%)	3 (15%)	5 (25%)	4.6	0.09
Rituximab	0 (0.0%)	0 (0.0%)	1 (5%)	2.0	0.3

Table (3) showed that there were statistically significant differences between the studied ITP patients in Received treatment. All Persistent ITP patients had received IVIG compared to 66.7% and 53.3% in newly diagnosed and chronic ITP patients. Almost two thirties of chronic ITP patients had received oral TPO compared to 33.3% and 0.0% in persistent and newly diagnosed ITP.

Table (4): Prognosis of the studied ITP patients

Prognosis	Newly diagnosed ITP (n=20)	Persistent ITP (n=20)	Chronic ITP (n=20)	P-value
Improvement	19 (95%)	12 (60.0%)	11 (55%)	**0.04 S**
No improvement	1 (5%)	8 (40.0%)	9 (45%)	

Table (4) showed that there were statistically significant differences between the studied ITP patients in Outcome. Newly diagnosed ITP patients had more improvement than both persistent and chronic ITP patients.

Table (5): Association between prognosis and general characteristics of the studied ITP patients:

Variables	Prognosis		P-value
	Improvement (n=41)	No improvement (n=19)	
Age (years): Mean ± SD Median	 6.0 ± 3.9 5.0	 9.2 ± 4.7 11.0	 **0.03 S**
Sex: Male Female	 20 (48.8%) 21 (51.6%)	 15 (78.9%) 4 (21.1%)	 0.06 **NS**
Weight (Kg): Mean ± SD Median	 21.8 ± 12.3 19.0	 32.9 ± 16.7 33.0	 **0.03 S**
Consanguinity: Positive Negative	 8(19.5%) 33 (80.4%)	 7 (36.9%) 12 (63.1%)	 0.2

Table (5) showed that there was a statistically significant association between prognosis and general characteristics of the studied ITP patients. Young age and less weight were associated with improvement. But regarding sex, there was no statistically significant association.

Table (6): Association between prognosis and received treatment of the studied ITP patients

Received treatment	Prognosis		χ^2	P-value
	Improvement (n=41)	No improvement (n=19)		
Corticosteroid	29 (70.7%)	15 (78.9%)	0.3	0.5
IVIG	31 (75.6%)	12 (63.1%)	0.9	0.4
TPO oral	8 (19.5%)	12 (63.1%)	8.8	**0.003(S)**
TPO SC	3 (7.3%)	5 (28.3%)	fisher	0.06

Table (6) showed that there was a statistically significant association between prognosis and Received treatment of the studied ITP patients. Oral TPO was associated with less improvement of ITP patients.

DISCUSSION

Immune (idiopathic) thrombocytopenic purpura (ITP) is an acquired organ-specific autoimmune thrombocytopenic syndrome in children characterized by immune-mediated platelet destruction due to binding of immunoglobulin (Ig) G autoantibodies against GpIIb/IIIa or GPIb/IX platelet glycoproteins. It is usually a benign, self-limiting disease in children. ITP incidence is 2–12/100 000 per year for adults and children, respectively, and a mortality rate of 1–3% per year in severely affected cases[7].

Dysfunction of T-cells in ITP may be contributed to the loss of tolerance, and impairment of the delicate balance of specific cytokine and serum cytokines may play a role in the pathogenesis of ITP [8].

So, the current case-control study was conducted on 60 ITP cases and 20 healthy controls at the Pediatric Hematology Unit and the outpatient clinic at Zagazig University Hospitals during the period from April 2020 to June 2021 to assess the prevalence, prognosis, and outcome of Egyptian children with primary immune thrombocytopenia.

The present study showed that was a statistically significant difference between the studied groups in age sex and weight. Chronic ITP patients had higher age, less weight, and more males and this was in agreement with the study of **Ebeid *et al.*** [8] where patients with chronic ITP were statistically older, with a mean age of 7.7±4.19 than those with acute ITP, with a mean age of 3.95±2.21($\chi 2$=3.83, P=0.001) and this is most probably because of the chronic nature of the disease as children with the chronic form of the disease are diagnosed for a much longer period, while children with acute ITP are usually diagnosed at a younger age.

In our study, there were statistically significant differences between the studied patients in follow-up Platelets count. Newly diagnosed ITP patients had the highest follow-up Platelets count followed by chronic ITP patients but regarding initial Platelets count, it was the least among Newly diagnosed ITP patients but this difference was not statistically significant, this was in agreement with **Ebeid *et al.*** [8] who found a statistically significant difference. Similarly, **Gözmen *et al.*** [9] found that the post-treatment platelet count was higher than the pre-treatment platelet count in the newly diagnosed ITP group (P<0.00). Eight patients had platelet counts higher than 150 000 cells/mm3, and six patients had platelet counts lower than 150 000 cells/mm3 in the post-treatment newly diagnosed ITP group.

Oppositely **Talaat *et al.*** [7], reported that ITP patients had a significant reduction in mean platelet count (P < 0·001) compared to control subjects, with maximum reduction in acute ITP (30 ±31·4) rather than chronic (77·2 ±44·6) subjects (P < 0·001).

Also, **Shalaby *et al.*** [12] was contrary to our finding and revealed a significant decrease in plasma IL7 level in both whole ITP patients and active ITP groups than the control group with median (interquartile range)(10 (5 - 20) versus 10 (5-15) versus 17.5 (5-30); p=0.016 respectively) and this result had its explanation by **Li *et al.*** [13] who suggested that the down-regulated IL7 in active ITP patients may be as a result of negative-feedback of up-regulated auto-reactive T cells since the auto-reactive T cells from ITP patients are resistant to apoptosis and expands more quickly than that of healthy controls.

The present study reported that were statistically significant differences between the studied ITP patients in Received treatment. All Persistent ITP patients had received IVIG compared to 66.7% and 53.3% in newly diagnosed and chronic ITP patients. Almost two thirties of chronic ITP patients had received oral TPO compared to 33.3% and 0.0% in persistent and newly diagnosed ITP and there were statistically significant differences between the studied ITP patients in Outcome as newly diagnosed ITP patients had more improvement than both persistent and chronic ITP patients, this was inconsistent with **Ebeid *et al.*** [8], On the follow-up of their patients with acute ITP over the study period, 70% of the patients had a complete remission, two were lost to follow-up at hematology clinic, and only one patient had a chronic progressive course.

CONCLUSION

Primary ITP in children is a nonthreatening and self-limited disease, usually lasting less than one year, and chronic form has different prognostic parameters. The use of these parameters can early distinguish children who are expected to have short and uneventful disease duration, to minimize their exposure to pharmaceutical intervention.

RECOMMENDATIONS

More multi-centric studies in the same direction are required involving a large sample size of patients to explore the exact etiology of ITP which may reveal their influence on the disease course, response to treatment, and the severity of bleeding.

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Conflict of interest: Nil.

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