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Study of Clinical Features and Laboratory Findings in Children with Immune Thrombocytopenia

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ABSTRACT

Background: Immune thrombocytopenia (ITP) is an autoimmune disease characterized by decreased platelet count in peripheral blood, which is caused by antibody production against surface antigens of platelets and their destruction by macrophages in reticuloendothelial system, as well as impaired thrombopoiesis. Reliable prediction of the course of the disease at time of diagnosis could be a useful tool regarding the planning of treatment, to minimize the risk of bleeding while avoiding drug complications.

Objective: This study aimed was to determine clinical features and laboratory findings in children with immune thrombocytopenia (ITP) among studied children.

Patients and Methods: This prospective cohort study included 48 patients categorized into 3 groups (acute, persistent and chronic). Acute group include 19 patients, persistent group include 11 patients and chronic group included 18 patients. The study was done in Hematology and Oncology Unit of Pediatric Department and Clinical Pathology Department, Zagazig University Hospitals.

Results: There was significant difference between the studied groups regarding platelet count initially at diagnosis, and after 6 months and percent change in platelet count at 6 months as compared to base line (on pairwise comparison, the difference is significant only between patients with acute and chronic ITP regarding change in platelet count. Also, the difference was significant between each individual groups regarding percent change in platelet count).

Conclusion: ITP in children is usually a benign disease with no or minimal bleeding. It has a high chance for spontaneous remission even without treatment. The most common presentation in ITP is cutaneous bleeding in form of petechiae and⁄or ecchymosis.

Keywords: Immune Thrombocytopenia, Clinical features, Laboratory findings.

INTRODUCTION

Immune thrombocytopenia (ITP) is autoimmune hematological disorder characterized by isolated thrombocytopenia (peripheral blood platelet count < 100×10^9/L) in absence of other causative systemic disorders. It is the most common cause of thrombocytopenia in children **(1).** The pathogenesis of ITP remains incompletely understood. The underlying mechanism is thought to be the reduced lifespan of platelets due to antibodies-mediated accelerated destruction by the reticuloendothelial system and abnormal production by bone marrow. Autoantibodies are directed against platelet surface glycoprotein antigens such as GPIIb /IIIa and GP Ib/ Ix complexes. This autoantibodies play a major rule in both platelet destruction and decrease platelet production **(2).**

ITP is characterized by wide variety of presentation, which range from skin and mucous membrane bleeding manifestation such as petechiae, purpura, bruising, epistaxis and gingival bleeding up to menorrhagia and intracranial bleeding. Intracranial bleeding is extremely rare, occurring in 0.5-1% of children when the platelet count drop below 10 x 10^9/L **(3).**

Diagnosis of ITP is made by a careful history, physical examination, complete blood count, and review of the blood smear. Response to initial treatment with corticosteroid or intravenous immunoglobulin (IVIG) supports the diagnosis and confirms the immune nature of the thrombocytopenia. However, additional investigation is necessary to exclude secondary thrombocytopenia and to provide additional information to assist with patient management **(4).** This study was designed to determine clinical features, laboratory findings in children with immune thrombocytopenia (ITP) among studied children.

PATIENTS AND METHODS

This was a prospective cohort study included 48 patients categorized into 3 groups (acute, persistent and chronic). Acute group include 19 patients, persistent group included 11 patients and chronic group included 18 patients. The study was done in Hematology and Oncology Unit of Pediatric Department and Clinical Pathology Department, Zagazig University Hospitals, during the period from March 2019 to August 2019 (6 months).

Sample size: The sample was calculated assuming that immune-thrombocytopenic patients presented at 8 /month. So, sample during 6 months was 48 patients. The patients were categorized into three groups according to their characters **(5)**. **Group 1,** acute ITP patients (less than 3 months from diagnosis), **group 2,** persistent ITP patients (from 3 months to one year from diagnosis), and **group 3,** chronic ITP patients (after one year from diagnosis).

Target population: All children with immune thrombocytopenia admitted to Hematology and Oncology Unit of Pediatric Department, Zagazig University Hospitals during the study period.

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Inclusion criteria: All children with immune thrombocytopenia (acute, chronic and persistent), and patients of both sex below the age of 14 years.

Exclusion criteria: Children with immune thrombocytopenia above 14 years, and children with thrombocytopenia due to other known causes such as collagen diseases, chronic infection and malignancies.

All patients were subjected to complete history taking, clinical examination and laboratory investigations according to The American Society of Hematology (ASH)[6] guidelines which include:

a) **Full history taking** (including onset, course, duration of ITP, age, gender, residence, history of preceded viral infection or vaccination and bleeding tendency without constitutional symptoms)
b) **Full general examination** with stress on hepatomegaly, splenomegaly and bleeding signs.
c) **Full clinical presentation and bleeding sign (**petechiae, ecchymosis, epistaxis, gingival hemorrhage, hematemesis, melena and menorrhagia or hematuria)
d) **Initial bleeding score:** Initial bleeding score in the patients was assessed according to type and site of bleeding and the Hb level at diagnosis [7]**.**
e) **Laboratory Investigations:**
    - Complete blood picture (initial and follow up (after 1, 3 and 6 months).
    - Thyroid function tests (T4-T3-TSH).
    - Level of immunoglobulins (IgG-IgA-IgM).
    - H.Pylori antigen in stool.
    - ANA, ADNAs.
    - Bone marrow aspiration when indicated.

Ethical consent:

Approval of the study was obtained from Pediatric Department after Institutional Review Board-Zagazig University (IRB-ZU). An informed consent was taken from every patient and his parent. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were expressed as means and standard deviations. Categorical variables were expressed as absolute frequencies and were compared using Chi square test and fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levine (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare medians of more than two groups, Kruskall-Wallis test (for non-normally distributed data) was used. One way ANOVA was used to compare change between means of more than two groups. To evaluate change over time in continuous variables, Friedman test was used for not normally distributed data. P value ≤ 0.05 was considered significant.

RESULTS

About 40% of the studied patients had acute ITP, while 37.5 % of them had chronic type and 22.9% had persistent type (Table 1).

Table (1): Distribution of the studied patients according to type of ITP

Type	N (48)	%
Acute	19	39.6
Chronic	18	37.5
Persistent	11	22.9

There was non-significant relation between outcome of the studied patients and either gender, age or residence (Table 2).

Table (2): Comparison between the studied groups regarding demographic characteristics

Demographic characteristics	Outcome of ITP			Test	
	Acute ITP	Persistent ITP	Chronic ITP	X^2	p
	N=19 (%)	N=11 (%)	N=18 (%)		
Gender:					
Male	11 (57.9)	4 (36.4)	12 (61.1)	1.86	0.465
Female	8 (42.1)	7 (63.6)	6 (38.9)		
Residence:					
Rural	15 (78.9)	8 (72.7)	12 (66.7)	0.707	0.716
Urban	4 (21.1)	3 (27.3)	6 (33.3)		
Age:					
Mean ± SD	6.5 ± 3.61	8.32 ± 4.66	8.78 ± 2.82	KW	
Median (Range**)**	6 (1 - 13)	11 (2 – 13)	8.5 (3 – 13)	5.315	0.07

KW Kruskall Wallis test

There was non-significant relation between the studied groups and history of risk factors (Table 3).

Table (3): Comparison between the studied patients regarding past history of risk factors

Risk factors	Outcome			Test	
	Acute ITP	Persistent ITP	Chronic ITP	X^2	p
	N=19 (%)	N=11 (%)	N=18 (%)		
Recent Vaccination:				3.027	0.261
No	16 (84.2)	10 (90.9)	18 (100)		
Yes	3 (15.8)	1 (9.1)	0 (0)		
Infection :					
No	10 (52.6)	8 (72.7)	13 (72.7)	4.064	0.434
URTI	7 (36.8)	3 (27.3)	5 (27.8)		
GE	2 (10.5)	0 (0)	0 (0)		
H. Pylori stool antigen:					
Negative	17 (89.5)	9 (81.8)	13 (72.2)	1.809	0.359
Positive	2 (10.5)	2 (18.2)	5 (27.8)		

There was non-significant difference between the studied groups regarding bleeding score and other hematological parameters (Table 4).

Table (4): Relation between patient outcome and hematological parameters

Clinical and laboratory parameters	Classification of ITP			Test	
	Acute ITP	Persistent ITP	Chronic ITP	KW	p
	N=19 (%)	N=11 (%)	N=18 (%)		
	Median (range)	Median (range)	Median (range)		
TLC	10 (5-34)	8.5 (5 – 19)	7.9 (5- 12)	2.66	0.265
	Mean ± SD	Mean ± SD	Mean± SD	F	p
Hemoglobin (g/dL)	10.74 ±1.37	10.91 ±1.69	11.45 ± 0.93	1.302	0.282
Bleeding score:	2.42 ± 0.61	2.45 ± 0.52	2.22 ± 0.65	0.696	0.504
1	1	0	2		
2	9	6	10	2.019	0.786
3	9	5	6		
	N=19 (%)	N=11 (%)	N=18 (%)	*X2*	p

There was significant difference between the studied groups regarding platelet count initially at diagnosis, after 6 months and at percent change in platelet count at 6 months as compared to base line (on pairwise comparison, the difference was significant only between patients with acute and chronic ITP regarding change in platelet count) (on pairwise comparison, the difference was significant between each individual group regarding percent change in platelet count) (Table 5).

Table (5): Relation between the studied groups regarding platelet count over time of follow up

Clinical and laboratory parameters	Classification of ITP			Test	
	Acute ITP	Persistent ITP	Chronic ITP	KW	p
	N=19 (%)	N=11 (%)	N=18 (%)		
	Median (range)	Median (range)	Median (range)		
Initially at diagnosis	**6 (0-52)**$^{\lozenge}$	**10 (2 – 94)**	**32.5 (4 – 75)**$^{\lozenge}$	**10.671**	**0.005***
After one month	**60 (21-510)**	**38 (3 – 167)**	**40 (10 – 140)**	**7.406**	**0.087**
After 3 months	**150 (4-404)**	**54 (5 - 245)**	**71.5 (15 – 163)**	**10.539**	**0.076**
After 6 months	**210 (10-350)**$^{\lozenge}$	**84 (8 – 420)**	**74 (9 – 280)**$^{\lozenge}$	**10.658**	**0.027***
Percent change at 6 months	**1625(139-34900)**	**950(84.48-12900)**	**184.3(-74.29-2875)**	**12.256**	**0.002***

KW Kruskall Wallis test *p<0.05 is statistically significant

There was non-significant difference between the studied groups regarding bleeding score and other hematological parameters **(**Table 6).

Table (6): Relation between patient outcome and hematological parameters

Clinical and laboratory parameters	Classification of ITP			Test	
	Acute ITP	Persistent ITP	Chronic ITP	KW	p
	N=19 (%)	N=11 (%)	N=18 (%)		
	Median (range)	Median (range)	Median (range)		
TLC	10 (5-34)	8.5 (5 – 19)	7.9 (5- 12)	2.66	0.265
	Mean ± SD	Mean ± SD	Mean ± SD	F	p
Hemoglobin	10.74 ±1.37	10.91 ±1.69	11.45 ± 0.93	1.302	0.282
Bleeding score:	2.42 ± 0.61	2.45 ± 0.52	2.22 ± 0.65	0.696	0.504
1	1	0	2		
2	9	6	10	2.019	0.786
3	9	5	6		
	N=19 (%)	N=11 (%)	N=18 (%)	*X2*	p

DISCUSSION

As regards acute group, in the present study, the majority of the studied cases were males (11/19, 57.9%), while 42.1% of cases were female (male predominance). **Badrawy *et al.*** [8] also found male predominance in newly diagnosed ITP. On contrary to the current result, **Makis *et al.*** [9] reported equal sex distribution among newly diagnosed cases. However **Eyada *et al.*** [10] found female predominance. This difference may come from their large number included in their study.

The ages of newly diagnosed cases in the present study ranged between 1 to 13 years old with median age of 6 years. This result is also supported by **Ahmed *et al.*** [11], who found that the median age of patients was 6 years. **Makis *et al.*** [9] similarly showed that the median age of incidence was 4.8 years in their retrospective study. On contrary to the current study, **Donato *et al.*** [12] observed peak predominance at first 2 years of age. The difference may be related to the number of patients as their study included large number than ours.

In the present study 79% of the patients were from rural areas. On contrary to this result**, Al-Zuhairy** [13] found that about two thirds of the patients diagnosed with ITP were living in urban areas.

Preceding infection or vaccination history has been reported as a frequent finding in childhood ITP.

Mucosal bleeding is an important presentation of ITP. In our study all cases presented by cutaneous bleeding, 47.4% of them presented with epistaxis and 57.9% of them presented by gingival hemorrhage, none of our patients developed intracranial hemorrhage (ICH) at diagnosis or during follow–up period. This agrees with the study of **Al-Zuhairy** [13] who showed that petechiae and/or bruising were the most common (92%) clinical features among children diagnosed with ITP followed by epistaxis (44%,) and oral bleeding (32%). In constant, the results of **Makis *et al.*** [9] reported that in the newly diagnosed, 30 of 43 children (70%) had mucosal bleeding. Also, 2 patients presented with conjunctival hemorrhage and only one patient presented with menorrhagia. No patient presented with hepatosplenomegaly.

At initial diagnosis, the mean platelet count was 12.42 x 10^9/L, this finding is similar to that reported in the study of **Al-Zuhairy** [13] which mean platelet count was 13.200 x10^9/L. This result is in contrast with **Makis *et al.*** [9] as the mean platelet count at diagnosis 5.5 × 10^9/L in acute ITP.

Our results showed no statistically significant correlation was found between laboratory findings and the course of the disease. This is in contrary with **Deel *et al.*** [14] who showed significant lower TLC in patients developing chronic ITP.

No patient had positive ANA or anti-dsDNA in this study. However, **Güngör *et al.*** [15] studied ANA and anti-dsDNA titration in 201 patients. They found that ANA returned positive titers in 6.9% of the patients and anti-dsDNA returned positive titers in 3.4% of the patients. **Heitink-Polle *et al.*** [16] reported that positive ANA is predictor factor for chronicity.

No patient had abnormal thyroid function test in this study. However, **Provan *et al.*** [17] reported that 8 to 14% of ITP patients who were followed up for long-time developed clinical hyperthyroidism. Others developed antibodies to thyroglobulin and may eventually develop hyper- or hypothyroidism. Mild thrombocytopenia has been reported in patients with hyperthyroidism (reduced platelet survival) and hypothyroidism (possible decreased platelet production), which often resolve with restoration of the euthyroid state. It may also be useful to measure antibodies to thyroglobulin and thyroid-stimulating hormone (TSH) to identify patients at risk for clinical thyroid disease

Bone marrow (BM) aspiration not done in 9 patients (47.3%) in acute presentation. 2 patients gave normocellular picture and the rest of patients (42.2%) give hypercellular picture with increase in megakaryocyte number. The study showed non-significant relation between bone marrow aspiration results and outcome. This result is supported by **Labarque and van Geet** [18] in which bone marrow aspiration not done in majority of acute ITP patients and if performed, the result of normal or increased number of immature megakaryocytes was seen in most patients.

Our study showed that only 10.5% of patients had no medication and treated by observation only, 78.9% received steroid therapy mainly oral therapy (57.9%). The same percentage 78.9% received IVIG therapy and about 73.7% received combined therapy. Only 2 patients received revolade and no one take immunosuppressive drugs. This result is similar to **Akbayram *et al.* [19]** which indicated that therapy was given to 95% of patients. While 5% of patients managed by observation only.

CONCLUSION

ITP in children is usually a benign disease with no or minimal bleeding. It has a high chance for spontaneous remission even without treatment. The most common presentation in ITP was cutaneous bleeding in form of petechiae and/or ecchymosis.

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