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ORIGINAL ARTICLE

Prognostic Value of Interleukin 17 in Patients with Auto Immune Thrombocytopenic Purpura

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Abstract

Background: ***Platelet breakdown and manufacturing issues are at the heart of immune thrombocytopenia, an autoimmune bleeding condition. Clinical features and laboratory tests performed after ruling out other disorders that cause thrombocytopenia are essential for making a diagnosis. In recent years, the pro-inflammatory cytokine interleukin 17 (IL-17) has been linked to autoimmune disease development.***

Aim and objectives: ***To evaluate the Prognostic Value of IL-17 in persons with various categories of immune thrombocytopenic Purpura.***

Subjects and methods: ***The current prospective trial included 90 patients with immune thrombocytopenia purpura who attended the haematology unit, internal medicine department, faculty of medicine, Al Hussein Hospital, and Al-Azhar University.***

Results: ***There was a statistically significant alteration amongst the examined groups (Evaluation among studied groups according to interleukin 17) and HB in Complete blood count. There was a significant connection between IL-17 and Age and Lymphadenopathy. There was a significant connection between HB and Age, Lymphadenopathy, and Lymphadenopathy. There was a significant association between Platelets and Lymphadenopathy, Age, and Lymphadenopathy.***

Conclusion: ***Egyptian children with Immune thrombocytopenic Purpura (ITP) have higher than average serum IL-17, suggesting a link between the two. Since blood IL-17 levels can predict the natural course of ITP and offer fresh insights into the pathophysiology of juvenile ITP, it may be useful to include it in the regular workup of children with Immune thrombocytopenic Purpura at the time of initial diagnosis.***

Keywords: Interleukin 17; Thrombocytopenic Purpura; Auto Immune

1. Introduction

Accelerated mucocutaneous bleeding and a peripheral platelet count (under 100x109/L) are hallmarks of immune thrombocytopenia, an autoimmune bleeding condition defined by accelerated platelet destruction and decreased platelet synthesis. [1]

Clinical symptoms and laboratory tests must rule out other conditions that cause thrombocytopenia in order to make a diagnosis of immune thrombocytopenia. [2]

Loss of immunological tolerance to self-antigens expressed on the surface of platelets and megakaryocytes characterizes the condition known as immune thrombocytopenia, which is associated with immune dysregulation.[3]

The 1ry cause of immune thrombocytopenia is Fc receptor (FcR)-mediated phagocytosis and death of immune cells by macrophages in the reticuloendothelial system of the spleen. [4]

People diagnosed with immune thrombocytopenia have anomalies in their bodies' CD4+ T cell subsets. In the acquired immune system, CD4+ T cells perform a crucial role by helping to promote the distinguishing and maturation of B cells, assisting in the development and proliferation of CD8+ T cells and other immune cells, and coordinating the interaction between various types of immune cells. As a result, CD4+ T lymphocytes play an essential role in developing autoimmune thyroiditis of the pancreas. [5]

The immunologic disruption typical of ITP can be made worse by the activation of Th17 cells, which stimulate the production of a variety of pro-inflammatory cytokines such as interleukin-6, interleukin-8, and granulocyte colony-stimulating factor. [6]

This work aimed to determine the Prognostic Value of IL-17 in persons with various categories of immune thrombocytopenic Purpura.

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2. Patients and methods

The current prospective research comprised ninety individuals with immune thrombocytopenia purpura treated at the Attending Hematology unit of the Internal Medicine Department at Al Hussein Hospital, which is affiliated with Al-Azhar University's Faculty of Medicine.

Inclusion criteria: Cases with immune thrombocytopenic Purpura presented with a history of bleeding tendency and Mucous membrane bleeding. Skin purpuric eruptions were confirmed by clinical examination and laboratory investigations.

Exclusion criteria: Medications linked to thrombocytopenia or a history of coexisting autoimmune illnesses, such as systemic lupus erythematosus (SLE); Patients with significant comorbidities or concomitant malignancies; and manifestations of active infection.

Eligible patients were divided into two groups: Group I, composed of 45 patients with chronic immune thrombocytopenic Purpura not responding to treatment, and Group II, composed of 45 patients with acute newly diagnosed immune thrombocytopenic Purpura on and without treatment.

All participants were subjected to Detailed history taking, Medical Diagnosis, laboratory investigations (Bone marrow examination (only for chronic cases not responsive to treatment), Complete blood count (CBC), and serum interleukin 17 levels by ELISA technique).

Sample Size

The sample size was determined using the same assumptions as the Hassan et al. study: a 95% two-sided confidence level and eighty per cent power. The error of five per cent &. The highest number of output samples taken was 82. To account for potential subjects dropping out during follow-up, the sample size was expanded to 90.[7]

Sample Size For Comparing Two Means

Input Data

Confidence Interval (2-sided)	95%
Power	80%
Ratio of sample size (Group 2/Group 1)	1

	Group 1	Group 2	Difference*
Mean	9.4	9.6	-0.2
Standard deviation	0.37	0.26	
Variance	0.1369	0.0676	

Sample size of Group 1	41
Sample size of Group 2	41
Total sample size	82

*Difference between the means

Results from OpenEpi, Version 3, open source calculator--SSMean
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

Bone marrow clots were stained with hematoxylin and eosin (HE) stains of 3-µm sections for morphological examination. Formalin-fixed and paraffin-embedded specimens were made for immunohistochemical analysis using antibodies for the IL-17. The IL-17 marker was defined as positively expressing when the entire cytoplasm, including nucleated cell membranes, was stained. Serum IL-17 levels were determined by the ELISA kit for human IL-17 purchased.

Prior to use, 1,000 µL of the top standard was prepared at a concentration of 250 pg/mL from the stock solution in 1X Assay Diluent A. Six two-fold serial dilutions of the 250 pg/mL top standard were performed with 1X Assay Diluent A in separate tubes. After diluting, the human IL-17 standard concentrations were 250 pg/mL, 125 pg/mL, 62.5 pg/mL, 31.3 pg/mL, 15.6 pg/mL, 7.8 pg/ mL, and 3.9 pg/mL, respectively. 1X Assay Diluent A was the zero standard (0 pg/mL).

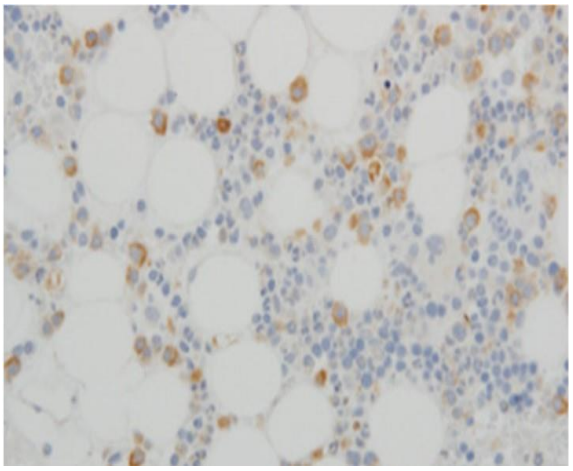

Fig 1: Hematoxylin and eosin (HE) section and immunohistochemical staining for IL-17

Statistical Analysis

SPSS version 23 was employed to perform information entry, validation, and analysis. The data from the present research was analyzed using the following statistical procedures.

The quantitative results were presented as mean + standard deviation (SD), whereas the qualitative data were presented as numbers and percentages.

The following statistical analyses were utilized for the contrast: the Mann-Whitney test, the student t-test, the Z-test for percentage, the Chi-square test (X2), and the odds ratio (OR).

3. Results

Table 1. Comparison amongst studied groups in accordance to demographic data

	GROUP I	GROUP II	P
AGE	7.62±0.49	6.42±0.5	0.89
SEX			0.39
MALE	28 (62.2%)	24 (53.3%)	
FEMALE	17 (37.8%)	21 (46.7%)	

This table shows that in Group I, the mean age was 7.62±0.49, there were 28 male. In Group I, the mean age was 6.42±0.5, there were 24 male. There was insignificant difference between both groups according to demographic data.

Table 2. Comparison between studied groups according to Clinical presentation

	GROUP I	GROUP II
PURPURA	41 (91.1%)	33 (73.3%)
ECCHYMOSIS	11 (24.4%)	28 (62.2%)
EXTERNAL BLEEDING	24 (53.3%)	31 (68.9%)
PALLOR	13 (28.9%)	24 (53.3%)
LYMPHADENOPATHY	30 (67.7%)	2 (4.4%)

This table shows that in Group I, there were 41 had Purpura, 11 had Ecchymosis, 24 had external bleeding, 13 had pallor, and 30 had lymphadenopathy. In Group II, there were 33 had Purpura, 28 had Ecchymosis, 31 had External bleeding, 24 had pallor, 2 had lymphadenopathy.

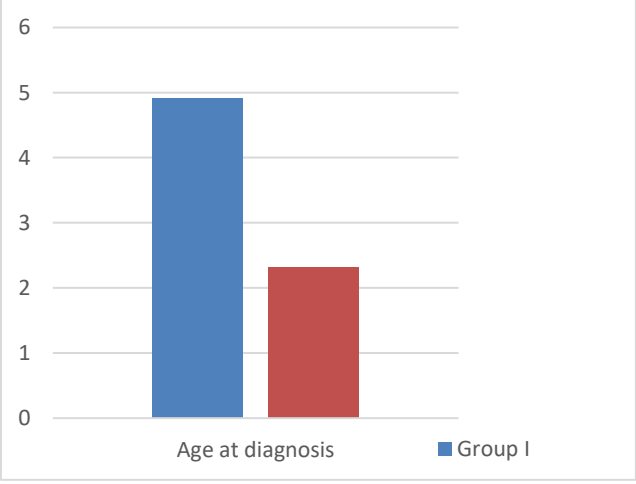

Figure 1. Comparison between studied groups according to age at diagnosis

Table 3. Comparison amongst studied groups depending on Complete blood count (CBC)

	GROUP I	GROUP II	P
HB (G/DL)	7.66±0.11	7.95±0.05	0.0001
WBCS(*109/L)	5±0.1	5±0.11	0.99
PLATELETS(*109/L)	22.4±1.1	18.44±1.1	0.99

This table displays that in Group I, the mean HB was 7.66±0.11, WBCs was 5±0.1 and Platelets was 22.4±1.1. In Group II, the mean HB was 7.95±0.05, WBCs was 5±0.11 and Platelets was 18.44±1.1. There was significant difference between both groups according to HB.

Table 4. Comparison among studied groups in accordance with IL17 levels

	GROUP I	GROUP II	P
IL17 LEVELS .	145.11±7.37	486.11±23.12	<0.00001

This table shows that in Group I, the mean IL17 levels were 145.11±7.37. In Group II, the mean IL17 486.11±23.12. There was high significant variance between both groups according to IL17 levels.

Table 5. Correlation among HB, WBCs, Platelets & IL17 also different parameters

CORRELATIONS

		HB	WBCs	Platelets	IL17
AGE	Pearson Correlation	-.679-**	0.45	.682**	-.772-**
	P value	0.000	0.55	0.000	0.000
MALE	Pearson Correlation	-0`.177	0.118	0.191	-0.139
	P value	0.095	0.081	0.071	0.190
FEMALE	Pearson Correlation	0.177	0.290	-0.191	0.139
	P value	0.095	0.095	0.071	0.190
PURPURA	Pearson Correlation	-0.121	0.16	0.126	-.230-*
	P value	0.258	0.27	0.238	0.029
ECCHYMOSIS	Pearson Correlation	-0.016	0.14	0.105	-0.143
	P value	0.879	0.22	0.327	0.180
EXTERNAL BLEEDING	Pearson Correlation	-0.114	0.055	0.053	-0.153
	P value	0.286	0.21	0.621	0.151
PALLOR	Pearson Correlation	-0.065	0.10	0.105	-0.189
	P value	0.544	0.21	0.324	0.074
LYMPHADENOPATHY	Pearson Correlation	-.376-**	0.18	.262*	-.384-**
	P value	0.000	0.51	0.013	0.000
AGE AT DIAGNOSIS	Pearson Correlation	-.832-**	0.13	.842**	-.960-**
	P value	0.000	0.24	0.000	0.000

*Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

b. Cannot be computed because at least one of the variables is constant.

There was significant correlation between IL17 and Age, Lymphadenopathy and Lymphadenopathy. There was significant correlation between HB and Age, Lymphadenopathy and Lymphadenopathy. There was significant correlation between Platelets and Age, Lymphadenopathy and Lymphadenopathy.

Table 6. ROC curve analysis of IL17 and CBC

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Cutoff	Sensitivity	Specificity	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
HB	.187	.049	7.650	71.11%	88.8%	.000	.092	.282
WBCs	.128	.041	3.9950	88.8%	100%	.000	.048	.207
Platelets	1.000	.000	21	71.1%	-	.000	1.000	1.000
IL17	.101	.033	152	91.1%	93.33%	.000	.035	.167

This table shows that the Sensitivity of IL17 was 91.1%, Specificity was 93.3%. The Sensitivity of Platelets was 71.1%. The Sensitivity of HB was 71.11%, Specificity was 88.8%.

4. Discussion

Children often develop an autoimmune thrombocytopenic condition known as immune thrombocytopenic Purpura. Autoantibodies of the immunoglobulin (Ig) G class bind to platelet glycoproteins (GPs), most often GPIIb/IIIa in addition to GPIX, and cause immune-mediated platelet death. In severe cases, the mortality rate from ITP is roughly one to three percent per year, with an annual incidence of around 12 per 100,000 children. [8]

The main results of this study were as follows:

According to demographic data, the mean Age in Group I was 7.62±0.49, and there were 28 male groups. The mean Age in Group II was 6.42±0.5, and there were 24 males. There was an insignificant difference between both groups.

Fifty individuals with ITP were included in our research, and 22 (44%), including 11 boys and 11 girls (50% each), met the criteria for chronic PIT; their mean age was 7.91± 3.37. Acute Immune thrombocytopenic Purpura affected 28 kids (56%) with a mean age of 6.29± 3.49 years; 16 boys and 12 girls were affected. In addition, a control group consisting of 50 youngsters of the same gender and age (28 boys and 22 girls, or 57.0% boys and 43.0% girls) served as a comparison. They averaged 7.42± 3.21 years old. There was an insignificant difference between both groups according to demographic data.[9]

The present study showed that, regarding clinical presentation, in Group I, 41 had Purpura, 11 had Ecchymosis, 24 had external bleeding, 13 had pallor, and 30 had Lymphadenopathy. In Group II, 33 had Purpura, 28 had Ecchymosis, 31 had External bleeding, 24 had pallor, and 2 had Lymphadenopathy.

While in the study of Zidan et al. Twenty children diagnosed with Immune thrombocytopenic Purpura (Patients' Group) and twenty Age- and sex-matched healthy subjects (Control Group) participated in this case-control trial. Five cases (25.0%) reported a history of fever before diagnosis; nineteen children (95.0%) displayed cutaneous manifestations; five individuals (20.0%) indicated a propensity to bleed; as well as no patients exhibited organomegaly.[1]

In the study of Hassan et al., as regards clinical presentation, Purpura in 46 (92%), Ecchymosis in 43 (86%) and External bleeding in 32 (64%) of their studied Group.[7]

FurthermoGroupmail et al.revealed that fifty per cent of the participants had a history of viral infections, and eighty per cent had some cutaneous bleeding (Purpura or Ecchymosis). Three-sixths of individuals experienced bleeding from the gums or nose (epistaxis). Two individuals with chronic ITP (3.3% of all cases) experienced intracranial bleeding due to their extreme thrombocytopenia.[10]

The current study showed that, regarding Age at diagnosis, the mean Age in Group I was 4.91±0.29. In Group II, the mean Age was 2.31±0.47. There was an insignificant difference between both groups according to Age at diagnosis.

However, in the study of Hassan et al., the mean age at diagnosis was 6.9 ± 2.14 years.

In the study in our hands, regarding CBC, the mean HB was 7.66±0.11 in Group I, WBCs were 5±0.1, and Platelets were 22.4±1.1. In Group II, the mean HB was 7.95±0.05, WBCs was 5±0.11, and Platelets was 18.44±1.1. There was a significant difference between both groups, according to HB.[7]

Soliman et al., in their investigation, corroborated our findings by showing that the Hb concentration was lower in those with ITP compared to controls.[11]

Our results showed that as regards IL-17, in Group I, the mean IL17 levels were 145.11±7.37. In Group II, the mean IL17 was 486.11±23.12. There was a significant alteration amongst both groups according to IL17 levels. There was a significant correlation between IL17 and AgeAge and between Lymphadenopathy and Lymphadenopathy. There was a significant connection between HB and AgeAge and between Lymphadenopathy and Lymphadenopathy. There was a significant correlation between platelets and AgeAge and Lymphadenopathy and Lymphadenopathy. Using ROC curve analysis of IL17 and CBC, the Sensitivity of IL17 was 91.1%, and Specificity was 93.3%. The Sensitivity of Platelets was 71.1%. The Sensitivity of HB was 71.11%, and Specificity was 88.8%.

Consistent with our findings, Hassan et al. observed that individuals participating in their research had considerably greater serum interleukin-17 levels than controls. Serum IL-17 levels were significantly inversely related to patient age. There was no statistically significant connection between AgeAge at diagnosis or platelet count and serum interleukin -17 levels.[7]

Up-regulation of Th17 cells, in addition to Th1, was initially documented among individuals with ITP by Zhang and colleagues in 2009. They hypothesized that Th17 cytokines favoured an imbalance favouring a more significant Th1-type immune response in ITP. [12]

Consistent with our findings, Ghallab et al. revealed significant variations in serum IL-17 levels among untreated ITP patients and the control group (91.5 vs. 59.9 pg/ml, p under

0.001).[13]

Immunogenicity is greatly enhanced by interleukin-17. Colony-stimulating factors, tumour necrosis factor-alpha, metalloproteinases, chemokines, and interleukin-6 are all released, helping mice and ITP patients produce more antiplatelet antibodies. Additionally, neutrophils are activated and mobilized by interleukin-17. One possible contributor to the development of ITP is IL-17, which either alone or in combination with B-cell activating factor (BAFF) protects B cells from apoptosis, enhances B-cell proliferation, as well as stimulates plasma cell differentiation.[13]

The CD4+Tcell subset known as Th17 has been linked to the development and progression of several autoimmune disorders. These conditions include rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Abnormal Th17 cells have been linked to ITP, a classical autoimmune illness. Individuals with active ITP have been reported to have significantly higher levels of Th17 cells compared to healthy controls. Through the secretion of interleukin-17 as well as IL-17F in response to IL-33, Th17 cells have the potential to stimulate the production of a variety of pro-inflammatory molecules, including IL-6, IL-8, as well as granulocyte colony-stimulating factor, which in turn exacerbates the immunologic disruption that is characteristic of ITP. [6]

The relatively small sample size enrolled in the trial and the fact that it was a single-centre study could be linked to the limitations of this investigation. As a result, additional research with more significant cohorts is recommended to validate the diagnostic function IL-17 among individuals with various categories of immune thrombocytopenic Purpura.

4. Conclusion

We noticed that interleukin -17 in the serum of Egyptian children with ITP was a predictor of their risk of developing the disease. Predicting the natural course of ITP and offering new insights into the aetiology of childhood ITP are possible outcomes of measuring blood IL-17 levels at the time of initial diagnosis.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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