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Evaluation of Pediatric Immune Thrombocytopenia (ITP) Cases and Risk Factors for Chronic ITP - Single Center Experience

Pediatrik İmmün Trombositopeni (İTP) Vakalarının ve Kronik İTP için Risk Faktörlerinin Değerlendirilmesi - Tek Merkez Deneyimi

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ABSTRACT

Aim: Immune thrombocytopenia (ITP) is the most common acquired bleeding disorder in childhood. The study aimed to assess the demographic and clinical characteristics, and treatment responses and to evaluate their effects on chronicity in pediatric ITP cases.
Material and Methods: Primary ITP patients aged 1 month to 18 years, who were diagnosed and followed up in the Pediatrics Clinic of Tokat Gaziosmanpaşa University Hospital between January 2010 and December 2018, were retrospectively analyzed.
Results: Thirty-eight patients with a diagnosis of primary ITP were included in the study. The mean age of the patients was 94.3±53.4 (14-199) months. The female/male ratio was 1. Twenty (57.1%) patients had acute ITP, and 15 (42.9%) patients had chronic ITP. There was no significant difference between the acute ITP group and the chronic ITP group in demographic, clinical features, laboratory findings, and treatment responses. In the first 12 months, the number of admissions with a platelet count of <20 000 /mm^3, the number of admissions requiring treatment, and the rate of treatment given during follow-up were significantly higher in the chronic ITP group (p=0.001, p=0.001, and p<0.001, respectively).
Conclusion: To be aware of the risk factors for the development of chronic ITP will lead to the identification of high-risk patients, decisions about treatment and follow-up, and prevent unnecessary interventions and anxiety that may occur in the patient and his/her family. According to the results of this study, frequent relapses in the first year after the diagnosis of ITP may be considered a marker for chronic ITP.
Keywords: Child; acute immune thrombocytopenia; chronic immune thrombocytopenia; risk factors.

ÖZ

Amaç: İmmün trombositopeni (İTP) çocukluk çağının en sık görülen edinilmiş kanama bozukluğudur. Bu çalışmada, pediatrik İTP vakalarında demografik ve klinik özellikler ile tedavi yanıtlarının incelenmesi ve bunların kronikleşmeye olan etkilerinin değerlendirilmesi amaçlandı.
Gereç ve Yöntemler: Ocak 2010 ve Aralık 2018 tarihleri arasında Tokat Gaziosmanpaşa Üniversitesi Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği'nde tanı alan ve takip edilen, 1 ay ile 18 yaş arası primer İTP hastaları geriye dönük olarak incelendi.
Bulgular: Primer İTP tanısı olan 38 hasta bu çalışmaya dahil edildi. Hastaların yaş ortalaması 94,3±53,4 (14-199) ay idi. Kız/erkek oranı 1 idi. 20 (%57,1) hastada akut İTP, 15 (%42,9) hastada kronik İTP vardı. Akut İTP grubu ile kronik İTP grubu arasında demografik, klinik özellikler, laboratuvar bulguları ve tedavi yanıtları açısından anlamlı bir farklılık yoktu. İlk 12 ayda trombosit sayısı <20.000 /mm^3 olan başvuru sayısı, tedavi gerektiren başvuru sayısı ve takipte tedavi verilme oranı kronik İTP grubunda anlamlı olarak daha yüksekti (sırasıyla, p=0.001, p=0.001 ve p<0.001).
Sonuç: Çocuklarda primer İTP'de kronikleşme için risk faktörlerinin bilinmesi, yüksek riskli hastaların tanımlanarak takip ve tedavinin planlanmasına, gereksiz girişimlerin, hasta ve ailesinde meydana gelebilecek anksiyetenin önüne geçilmesine yardımcı olacaktır. Bu çalışmanın sonuçlarına göre, İTP hastalarında tanı sonrası ilk bir yıl içinde trombositopeni ataklarının sık görülmesi, kronik İTP için bir belirteç olarak kabul edilebilir.
Anahtar kelimeler: Çocuk; akut immün trombositopeni; kronik immün trombositopeni; risk faktörleri.

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INTRODUCTION

Immune thrombocytopenia (ITP) is an immune-mediated, acquired, common hematological disease characterized by decreased platelet count (<100 000 /mm3) and increased bleeding risk due to autoantibodies against platelets. ITP is classified as primary and secondary according to the presence of an underlying disease (1). Primary ITP is a diagnosis of exclusion and characterized by isolated thrombocytopenia in the absence of other causes which may be associated with thrombocytopenia such as systemic lupus erythematosus, Hepatitis C infection, or lymphoproliferative diseases (2). Another classification is based on the duration of the disease as newly diagnosed, persistent, or chronic ITP. Patients recovering from the disease within three months are defined as newly diagnosed/acute ITP whereas cases with persistent thrombocytopenia more than 12 months are defined as chronic ITP. Risk factors for chronic ITP were frequently studied in the literature and gender, age, degree of thrombocytopenia at admission, preceding viral infection or vaccination history, and sudden onset were found significant in some studies (3).

ITP is a benign disease and serious life-threatening bleeding such as intracranial hemorrhage in ITP patients is extremely rare, 0.6-1% (4-6). However, it is known that the disease is associated with some degree of anxiety and decreased quality of life especially in chronic ITP, both for the patient and his/her family (7-9). Therefore, identifying the risk factors and high-risk patients for chronic ITP and predicting the course of the disease is important for preventing unnecessary interventions and anxiety that may occur in the patient and his/her family.

In this study, we aimed to investigate the demographic, clinical, and laboratory characteristics, treatment responses, and risk factors for chronic ITP in children diagnosed and followed up in our center between 2010 and 2018.

MATERIAL AND METHODS

In this study, 38 patients aged between 1 month and 18 years who were diagnosed with primary ITP between January 2010 and December 2018 in Tokat Gaziosmanpaşa University Hospital, Department of Pediatrics were included. To create the list of patients, we performed a search via the International Classification of Diseases (ICD) codes. Codes covering 'purpura and other hemorrhagic conditions' (D69.0-D69.9) including primary ITP code (D69.3) were searched and the files of the patients with primary ITP were examined (Figure 1). Demographic information, clinical and laboratory findings, and treatments given to these patients were recorded. Among the platelet indices; mean platelet volume (MPV), platelet percentage in the blood (plateletcrit, PCT), platelet distribution width (PDW), the ratio of large platelets to normal ones (platelet large cell ratio, PLCR), and platelet mass index (PMI, platelet count multiplied by MPV) were evaluated. Exclusion criteria in the study were having the diagnosis in another center and secondary thrombocytopenia. The study was approved by the Ethics Committee of Tokat Gaziosmanpaşa University (04.12.2018, 276).

Statistical Analysis

IBM SPSS Statistics 19.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.) was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, frequency), the Chi-square test was used in the comparison of qualitative data between groups. The Shapiro-Wilk test was used to evaluate the normality of the data. Levene's test was used to determine the homogeneity. For comparing the means of quantitative variables between groups, independent samples t test for normally distributed variables and Mann-Whitney U test for non-normal distributed variables were used. Pearson correlation coefficient was used for the strength and direction of the linear relationship between the variables. A p value <0.05 was considered significant.

RESULTS

A total of 38 patients diagnosed with primary ITP were included in this study. The female/male ratio was 1. The mean age was 94.3±53.4 (14-199) months. Signs of bleeding were present in 34 (89.4%) of the patients at the time of admission, there was one patient with severe bleeding (menorrhagia). The most common physical finding was ecchymosis on the skin which was present in 18 (47.3%) patients. Preceding infection was detected in 21 (55.2%) patients and the most common was upper respiratory tract infection. The general characteristics of the patients were given in Table 1.

Records of three patients were not sufficient for determining the course and discriminating between acute and chronic ITP and these were excluded in the comparison of acute and chronic ITP groups due to the uncertainty of course. Among the remaining 35 patients, 20 (57.1%) had acute ITP, 15 (42.9%) had chronic ITP, and no patient had persistent ITP. Comparison between acute and chronic ITP groups revealed no significant difference in demographic, clinical, or laboratory parameters (Tables 2 and 3).

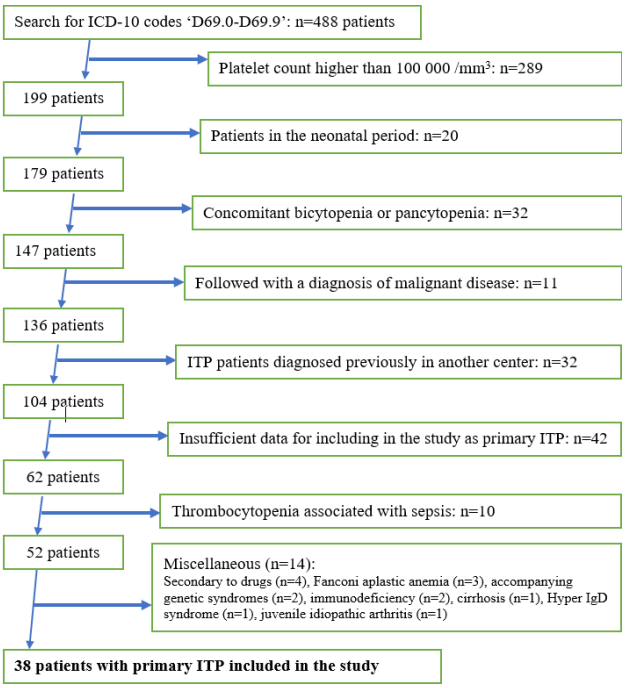

Figure 1. Identification of study patients
ITP: Immune thrombocytopenia, Ig: Immunoglobulin

Intravenous immunoglobulin (IVIG) was administered to 35 of 38 (92.1%) patients as initial therapy, and three patients were followed without pharmacological treatment. Among those 35 patients, three patients' records were not sufficient for discriminating between acute and chronic ITP. Of the remaining 32 patients, 19 (59.4%) were acute ITP, and 13 (40.6%) were chronic ITP. Two of the three patients who were followed up without treatment had chronic ITP, and one patient remained with acute ITP (Figure 2). In total, there were 20 (19 IVIG, 1 without treatment) patients in the acute ITP group, and 15 (13 IVIG, 2 without treatment) patients in the chronic ITP group. There was no significant difference between the acute and chronic ITP groups in IVIG doses (p=0.853), and platelet counts which were measured at 24, 48, and 72 hours after IVIG treatment (p values were 0.137, 0.610, and 0.498, respectively). In the chronic ITP group, during the first 12 months after diagnosis, the number of admissions with a platelet count under 20 000 /mm^3 and the number of admissions requiring treatment was significantly higher than in the acute ITP group (both p values were 0.001, Table 4).

In the chronic ITP group, during follow-up, 4 (26.7%) patients received IVIG treatment, 8 patients (53.3%) received IVIG + steroid treatment, and splenectomy was performed in 3 (20.0%) patients in whom remission was achieved. The rate of receiving medical treatment during follow-up in the chronic ITP group was significantly higher than in the acute ITP group (p<0.001).

In the study, in the acute ITP group, there was a strong negative correlation between the erythrocyte sedimentation rate (ESR) measured at the time of diagnosis and the platelet count at 72 hours after IVIG treatment (r=-0.980, p=0.012). In the same group, a strong

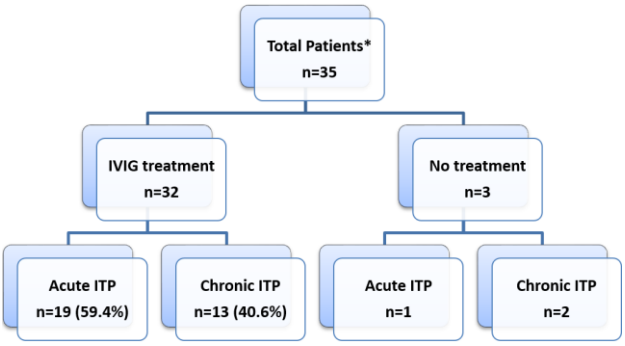

Figure 2. The course of the study patients according to initial treatment

*: The notes of three patients were not sufficient to decide about the course and they were not included in this figure. ITP: immune thrombocytopenia, IVIG: intravenous immunoglobulin

Table 1. Demographic and clinical features of the study patients (n=38)

Age groups, n (%)	
<24 months	5 (13.1)
24-72 months	9 (23.7)
>72 months	24 (63.2)
Gender (male), n (%)	19 (50.0)
Positive bleeding signs in PE, n (%)	34 (89.4)
Symptoms/signs at presentation, n (%)	
Petechia and purpura on skin	9 (23.7)
Ecchymosis on skin	18 (47.4)
Epistaxis	6 (15.8)
Menorrhagia	1 (2.6)
No bleeding sign	4 (10.5)
Thrombocytopenia detected incidentally	2 (5.3)
Fatigue	1 (2.6)
Abdominal pain	1 (2.6)
Previous infection history, n (%)	21 (55.2)
Upper respiratory tract infection	17 (44.8)
Acute gastroenteritis	3 (7.9)
Pneumonia	1 (2.6)
Season at presentation, n (%)	
Spring	8 (21.1)
Summer	11 (28.9)
Autumn	9 (23.7)
Winter	10 (26.3)

SD: standard deviation, min: minimum, max: maximum, PE: physical examination

Table 2. Comparison of demographic and clinical characteristics between acute and chronic ITP groups

	Acute ITP (n=20)	Chronic ITP (n=15)	p
Gender (male), n (%)	8 (40)	8 (53.3)	0.433
Age (months), mean±SD (min-max)	81.7±47.3 (17-158)	101.0±51.9 (14-175)	0.260
Age groups, n (%)			
<24 months	4 (20)	1 (6.7)	
24-72 months	4 (20)	4 (26.7)	0.696
>72 months	12 (60)	10 (66.7)	
Season at presentation, n (%)			
Spring	4 (20)	2 (13.3)	
Summer	6 (30)	5 (33.3)	0.967
Autumn	4 (20)	4 (26.7)	
Winter	6 (30)	4 (26.7)	
Positive bleeding signs in PE, n (%)	19 (95)	12 (80.0)	0.250
Symptoms/signs at presentation, n (%)			
Petechia and purpura on skin	6 (30)	1 (6.7)	
Ecchymosis on skin	10 (50)	8 (53.3)	0.346
Epistaxis	2 (10)	3 (20.0)	
Menorrhagia	1 (5)	0 (0.0)	
Previous infection history, n (%)	13 (65)	6 (40)	0.142

ITP: immune thrombocytopenia, SD: standard deviation, min: minimum, max: maximum, PE: physical examination

Table 3. Comparison of the laboratory parameters at the time of diagnosis between acute and chronic ITP groups

	Acute ITP (n=20)	Chronic ITP (n=15)	p
Hb (g/dl)	11.99±1.98	12.57±1.20	0.325
HTC (%)	35.12±5.70	37.41±3.06	0.169
PLT (/mm^3)	14139.00±12747.07	14182.67±11730.99	0.992
MPV (fL)	11.06±1.64	14.50	-
PMI	290.65±148.68	567.00	-
PCT (%)	0.03 (0.02-0.04) [0.01-0.05]	0.03 (0-0.06) [0-0.06]	0.999
PDW (fL)	19.58±4.14	20.60±2.39	0.759
CRP (mg/L)	3.19 (0.7-4.1) [0.1-22]	3.2 (0.6-5.6) [0.1-54]	0.900
ESR (mm/hour)	13.5 (3-23) [2-33]	7 (4-19) [2-45]	0.852
ALT (u/L)	19.73±14.67	15.19±4.10	0.325
AST (u/L)	31.46±21.98	28.00±6.07	0.600

ITP: immune thrombocytopenia, Hb: hemoglobin, HTC: hematocrit, PLT: platelet count, MPV: mean platelet volume, PMI: platelet mass index [PLT (/mm3) x MPV (fl)], PCT: plateletcrit, PDW: platelet distribution width, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, data were shown as mean±standard deviation or median (25th-75th percentile) [minimum-maximum]

Table 4. Comparison of IVIG doses and response to treatment between acute and chronic ITP groups

	Acute ITP (n=20)	Chronic ITP (n=15)	p
Dose of IVIG (g/kg)	0.88±0.15	0.87±0.20	0.853
PLT at 24th hour of IVIG treatment (/mm^3)	32.000±16.700	47.580±26.450	0.137
PLT at 48th hour of IVIG treatment (/mm^3)	75.830±45.340	91.600±81.450	0.610
PLT at 72nd hour of IVIG treatment (/mm^3)	145.690±82.300	119.650±75.890	0.498
Number of admissions with PLT <20 000 /mm^3 in the first 12 months	0 (0-0) [0-0]	2 (0-4) [0-14]	**0.001**
Number of admissions requiring treatment in the first 12 months	0 (0-0) [0-0]	1 (0-4) [0-10]	**0.001**

IVIG: intravenous immunoglobulin, ITP: immune thrombocytopenia, PLT: platelet, data were shown as mean±standard deviation or median (25th-75th percentile) [minimum-maximum]

positive correlation was found between the PCT value at the time of diagnosis and the platelet count at the 24th hour after IVIG treatment (r=0.925, p=0.008). In the chronic ITP group, a strong positive correlation was found between platelet counts at the time of diagnosis and at 24 and 48 hours after IVIG treatment (r=0.789, p=0.011, and r=0.743, p=0.022, respectively).

DISCUSSION

ITP is the most common cause of acquired thrombocytopenia in childhood and is characterized by shortened platelet lifespan due to immune-mediated platelet destruction in the reticuloendothelial system, isolated thrombocytopenia, and increased megakaryocytes in the bone marrow. Although primary ITP is a benign disease with a remission rate of 65-80% in children, it is known that it may become chronic at a rate of 25-30% (4). In the current study, demographic features, clinical characteristics, and laboratory findings at the time of diagnosis were not statistically different between acute and chronic ITP groups. In literature, possible factors related to the development of chronic ITP have been widely investigated. In a prospective study, Edslev et al. (10) found that symptoms lasting less than 2 weeks, age <10 years at diagnosis, preceding infection history, platelet count <5 000 /mm^3 at diagnosis, purpuric rash on mucous membranes and male gender were associated with improvement in the first 12 months in children with newly diagnosed ITP. In another study, abrupt onset and age under five years were found to be factors reducing the development of chronic ITP (11). In a systematic review and meta-analysis; female gender, age ≥11, no previous infection or vaccination history, insidious onset, platelet count ≥20 000 /mm^3 at diagnosis, and ANA positivity were associated with chronic ITP while mucosal bleeding was found to be related to decreased risk for chronic ITP (12). Similarly; female gender, age >10 years, no preceding infection, and platelet count ≥20 000 /mm³ at the time of diagnosis were found to be risk factors for chronic ITP in some recent studies (13-15).

The effect of initial treatment on the course of the disease has also been widely assessed in the literature. In general, it is considered that there is no relation between the treatment regimen and the natural course of ITP. However, in some recent studies, it is suggested that the agents used in treatment may have different effects. Some studies have shown that initial IVIG treatment reduces the development of chronic ITP (15-18) whereas others have found that it has an increasing effect (19) and some suggested it has no effect on chronicity (13,20,21). In a study from Thailand, it was found that pediatric ITP patients who were followed without treatment or who received steroids alone had less chronic ITP than those who received combined IVIG and methylprednisolone therapy (11). From Türkiye, Yıldız et al. (22) found that the relapse rate was lower in the untreated group than in the treated patients. In a

randomized controlled trial by Heitink-Polle et al. (18), initial treatment with IVIG was associated with decreased chronic ITP rate compared to follow-up without treatment. In our center, since IVIG was the first-line treatment and except for three cases followed without treatment vast majority of the patients were initially given IVIG, it was not possible to evaluate the effect of treatment on the development of chronic ITP.

In this study, among the patients who received IVIG initially, the rate of chronic ITP was found as 42.9% which is quite higher than the literature. This study was a retrospective study and the patients were identified by searching ICD codes. Probably the rate of correct recording of the ICD code and detection in the retrospective search was higher in chronic ITP patients who were admitted many times and received treatment with frequent relapses, compared to patients who were followed up without treatment and spontaneously improved. In addition, we think that some patients whose file notes were not sufficient and therefore not included in the study, may actually be acute ITP who were followed up without treatment and recovered spontaneously. All these factors may have contributed to the high rate of chronic ITP in this study.

In the current study, there was an important difference between acute and chronic ITP groups in the number of admissions. In the first 12 months after diagnosis, the number of admissions requiring treatment or admissions with a platelet count of <20 000 /mm3 was significantly higher in the chronic ITP group than the acute ITP group. Accordingly, frequent relapses after the diagnosis may be a predictor for chronic ITP.

It is known that some of the platelet indices are helpful in the diagnosis of ITP, and many studies have reported that they are useful in distinguishing between ITP and other causes of thrombocytopenia, especially hematological malignancies (23,24). However, there are few studies on the prognostic importance of these indices in ITP. In the study of Ahmed et al. (25), it was found that the rate of relapse and chronic ITP is lower in children if MPV is <8 fL at the time of diagnosis. Similarly, some adult studies have reported that MPV may be a marker for ITP relapse (26,27). In the study by Adly et al. (28), it was stated that the immature platelet fraction at admission was higher in chronic ITP patients than in acute ITP patients, and this parameter could be a marker for chronic ITP. In the current study, no significant difference was found between acute and chronic ITP groups for thrombocyte indices PDW, PCT, MPV, and PMI but this may be related to the small sample size of the study population. Since these indices are cheap and easy to work, we think that studies on the relation between these and chronic ITP with large patient groups will be valuable and promising.

In this study, we found a strong negative correlation between the ESR at admission and the platelet count at 72 hours after IVIG treatment in the acute ITP group. Although the acute-chronic course of the disease could not be known at presentation, these parameters may help predict the early IVIG response in patients.

This study has some limitations. The most important limitation is that it was a retrospective study which also led to the low number of study patients. We think some of the primary ITP patients missed out due to the shortcomings in the recording of ICD codes and inadequate file notes. Consequently, the rate of patients who received treatment and the rate of chronic ITP were higher than most of the studies in the literature.

CONCLUSION

In children with primary ITP being aware of the risk factors for the development of chronic ITP will lead to the identification of high-risk patients, decisions about treatment, prevent unnecessary interventions and anxiety that may occur in the patient and his/her family. According to the results of this study, frequent relapses in the first year after the diagnosis of ITP may be considered as a marker for chronic ITP. Prospective studies with large patient series are needed to determine clinical and laboratory risk factors more accurately.

Ethics Committee Approval: The study was approved by the Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University (04.12.2018, 276).

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All authors studied at Tokat Gaziosmanpaşa University School of Medicine at the time of the study.

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