Initial Lymphocyte Count as Prognostic Indicator for Childhood Immune Thrombocytopenia

Sinan Akbayram¹ · Kamuran Karaman¹ · Murat Dogan² · Lokman Ustyo² · Mesut Garipardic¹ · Ahmet Faik Oner¹

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Abstract Acute ITP is a benign, self-limiting disease. Chronic ITP is diagnosed when thrombocytopenia persists beyond 12 months. The main objective of the present study was to examine whether absolute lymphocyte counts at diagnosis has predictive value with chronic ITP. A total of 601 patients diagnosed as ITP between 1995 and 2014 were retrospectively evaluated. CBCs with differential counts were performed at presentation for 601 patients. Absolute lymphocyte counts at presentation were independently predictive of disease duration. The male to female ratio was almost 1:1 and 25.9 % (156/601) of the patients had chronic ITP. We determined that age >6.75 year, platelet counts >6.950/mm³ and absolute lymphocyte counts ≤2.050/mm³ was associated with a significant risk for developing chronic ITP. Absolute lymphocyte counts at the time of diagnosis were predictive variables for the development of chronic ITP. Further researches are needed to confirm the current finding and to assess the underlying pathophysiology with the course of the ITP in observational studies.

Keywords Child · ITP · Absolute lymphocyte counts

Introduction

Immune thrombocytopenic purpura (ITP) is one of the most common acquired bleeding disorders of childhood. ITP is a hemorrhagic disorder characterized by low platelet counts, spontaneous bruising, purpuric or petechial rash and mucosal bleeding [1]. Between 70 and 80 % of the cases are acute and spontaneously resolve within 1 year of presentation. The remaining 20–30 % of the cases are classified as chronic ITP, which is formally defined as having low platelet counts for 1 year after diagnosis [2]. ITP is an immune-mediated disorder in which circulating antiplatelet antibodies target epitopes on the platelet membrane [3]. Recent studies have demonstrated that the pathogenesis of ITP involves multifactorial autoimmune mechanisms of both humoral and cellular immunity and that acute and chronic forms may represent two distinct immunopathological disorders [4, 5]. Although lymphocytopenia is a commonly reported feature of many chronic autoimmune disorders, differential white-cell counts at presentation have seldom been evaluated as predictors for the development of childhood chronic ITP [6, 7].

The main objective of the present study was to examine whether absolute lymphocyte counts (ALC) at diagnosis correlate with the course of the ITP.

Patient Characteristics and Method

A total of 601 patients diagnosed as ITP between 1995 and 2014 in the Department of Pediatric Hematology, Faculty of Medicine, Yuzuncu Yil University were retrospectively evaluated. Patient's age, gender, platelet count, total leukocyte count and ALC at diagnosis were recorded.

✉ Kamuran Karaman
kamuran_karaman@hotmail.com

¹ Department of Pediatric Hematology, Yuzuncu Yil University, Van, Turkey

² Department of Pediatrics, Yuzuncu Yil University, Van, Turkey

The definitions suggested by the International Working Group (IWG) consensus panel in 2007 were used to define the course of ITP: “newly diagnosed” for all cases at diagnosis, and “chronic” for cases persisting >12 months [2].

Calculations and Statistical Analysis

Statistical analyses were performed using the commercial SPSS 14 package software. Conformity of continuous variables to normal distribution was assessed using the one-sample Kolmogorov–Simirnov test. For descriptive statistics, mean values were used for the variables with normal distribution, and median values were used for the variables without normal distribution. Parameters with normal distribution were compared using the variance analysis. Following variance analysis, the Duncan test was used to find the differences between the groups. The Chi square tests and receiver operating characteristic (ROC) curves were used to determine the relationship between categorical variables, and Z-test was used to compare the ratios. Level of significance was set as $p < 0.05$.

Results

A total of 601 patients with ITP were identified between 1995 and 2014. Of the 601 patients, 156 (25.9 %) had the disease for more than 12 months and were thus defined as

having chronic ITP. The conditions of the remaining 445 patients (74.1 %) resolved completely within 12 months and met the criteria for acute ITP. Table 1 shows the demographic features for the study groups. The male/female ratio of the children with acute and chronic ITP was not statistically significant ($p > 0.05$).

The children with chronic ITP presented at older ages than the children with acute ITP. The mean age (SD) at presentation for acute patients was 7.5 (4.4) and 8.25 (4.5) years for chronic patients, with a significant difference between the groups ($p = 0.03$).

18.3 % of those >6.75 years of age developed chronic disease, while only 7.6 % of those ≤6.75 years of age had ITP lasting beyond 12 months [OR 1.33, CI (0.91, 1.93); Table 2].

Platelet count at presentation ranged from low ($130/\text{mm}^3$) to a high ($96,500/\text{mm}^3$). The mean presenting platelet count (SD) for chronic ITP was higher $24,770/\text{mm}^3$ ($24,670/\text{mm}^3$) than that for acute ITP $22,000/\text{mm}^3$ ($27,060/\text{mm}^3$). There was a significant difference between acute and chronic cases ($p = 0.004$). However, only 7 % of patients with a platelet count $<6950/\text{mm}^3$ developed chronic ITP, while 18.9 % of those with a platelet count $>6950/\text{mm}^3$ followed a chronic course [OR 1.92, CI (1.28, 2.89); Table 2].

ALC at presentation ranged from a low ($300/\text{mm}^3$) to a high ($9,300/\text{mm}^3$). The mean presenting ALC for acute ITP and chronic ITP were $3,380 \pm 1,920/\text{mm}^3$ and $2,820 \pm 1,580/\text{mm}^3$, respectively. There was a significant difference between acute and chronic cases ($p = 0.02$). However, 10.6 % of patients with a ALC $\leq 2050/\text{mm}^3$ developed chronic ITP, while 15.3 % of those with a ALC $>2050/\text{mm}^3$ followed a chronic course [OR 2.42, CI (1.37, 4.50); Table 2]. The ALC cut-off value sensitivity was 56 %, specificity was 76 %, and positive predictive value (PPV) and negative predictive value (NPV) were 55.2 and 66.9 %, respectively.

Based upon univariate analysis, mean values of ALC, platelet count and age were found to be significantly different between the study groups (Table 1). The non-parametric multivariate analysis showed that a low ALC ($p = 0.002$), high platelet count ($p = 0.004$) and high age ($p = 0.004$) at presentation were associated with an increased risk for developing persistent ITP beyond

Table 1 Demographic features of the study groups

	Chronic	Acute	<i>p</i> value
Gender			
Male	80 (51.2 %)	226 (50.7 %)	>0.05
Female	76 (48.7 %)	219 (49.2 %)	>0.05
Age (years)			
Mean $\pm$ SD	8.25 $\pm$ 4.50	7.50 $\pm$ 4.48	0.03
TLC ($/\text{mm}^3$)			
Mean $\pm$ SD	9.280 $\pm$ 4.850	9.670 $\pm$ 4.340	>0.05
ALC ($/\text{mm}^3$)			
Mean $\pm$ SD	2.820 $\pm$ 1.580	3.380 $\pm$ 1.920	0.02
Platelet count ($/\text{mm}^3$)			
Mean $\pm$ SD	24.770 $\pm$ 24.670	22.000 $\pm$ 27.060	0.004

TLC total leukocyte count; ALC absolute lymphocyte counts

Table 2 The relationship between ITP outcome and the ALC, platelet counts and age cut-off values

	ALC (cell/mm^3)				Platelet counts (cell/mm^3)				Age (years)			
	≤ 2050	>2050	OR (95 %CI)	<i>p</i>	≤ 6950	>6950	OR (95 %CI)	<i>p</i>	≤ 6.75	>6.75	OR (95 %CI)	<i>p</i>
Acute ITP	126	318	2.492	0.002	263	182	1.92	0.004	255	200	1.331	0.004
Chronic ITP	64	92	(1.378–4.509)		42	114	(1.28–2.89)		46	110	(0.918–1.930)	

12 months (Table 2). ROC analysis was performed and confirmed that lower ALC and higher platelet counts and high age at presentation were helpful in predicting the persistence of ITP beyond 12 months.

Discussion

This study revealed that 74 % of the patients had acute ITP and 26 % had chronic ITP. Other studies have reported acute ITP percentages of 70–80 % and chronic ITP percentages of 20–30 % [1, 8]. No gender preference was observed as reported by several epidemiologic studies, with no gender risk for the development of chronic ITP [7–10]. In this study, ITP occurred with equal frequency in males and females, and no gender preference was found as a risk for chronicity ($p > 0.05$).

Watts [11] analyzed the data on 409 children with ITP. Chronic ITP with patients presented at an older age (7.8 vs 5.2 years for acute only, $p < 0.001$), and with higher platelet counts ($27.000/\text{mm}^3$ vs $17.000/\text{mm}^3$, $p < 0.001$). Granz et al. [1] demonstrated that patients with older age, and initial platelet counts $>20.000/\text{mm}^3$ were at risk for developing chronic ITP. Our study revealed chronic ITP with patients presented at an older age (8.2 vs 7.5 years for acute only, $p = 0.03$) also mean presenting platelet count (SD) for chronic ITP was higher $24.770/\text{mm}^3$ ($24.670/\text{mm}^3$) than that for acute ITP $22.000/\text{mm}^3$ ($27.600/\text{mm}^3$). There was a significant difference between acute and chronic ITP ($p = 0.004$).

Culic et al. [12] found an inverse correlation of ALC at diagnosis of ITP and platelet count in adult patients and suggested that a high ALC may be predictive of a poor prognosis in adult ITP patients; however, ALC at presentation were seldom evaluated in pediatric patients with ITP. Ahmed et al. [7] determined in pediatric ITP patients that ages >8.5 years and $\text{ALC} \leq 3.050/\text{mm}^3$ were associated with a significant risk for developing persistent ITP beyond 6 months. In another pediatric study, Deel et al. [6] found that ALC values at presentation were not independently predictive of disease duration. However, ALC values at 3 months were significant predictors. Sixty-eight percent (40/59) of patients >8 years of age and 43 % (20/46) of patients <8 years who had an $\text{ALC} \leq 3.000/\text{mm}^3$ at 3 months developed chronic ITP. This compares to chronic rates of only 25 % (3/12) and 2 % (2/87) of patients >8 and ≤ 8 years, respectively, with an $\text{ALC} > 3.000/\text{mm}^3$ at 3 months. Further, 92 % (60/65) of patients who developed chronic ITP had a 3-month $\text{ALC} \leq 3.000/\text{mm}^3$. An $\text{ALC} > 3.000/\text{mm}^3$ at 3 months is a strong predictor for platelet recovery, as only 5 % (5/99) of these patients developed

chronic ITP. This study suggests that progression to lower lymphocyte counts over the first few months of disease is a strong predictor for chronic ITP. Our study demonstrated that ALC values ($\text{ALC} \leq 2050/\text{mm}^3$) at presentation were independently predictive of disease duration. Of patients with a platelet count $\leq 6950/\text{mm}^3$, 13.7 % developed chronic ITP, while 38.5 % of those with a platelet count $>6950/\text{mm}^3$ followed a chronic course [OR 1.92, CI (1.28, 2.89)]. Of patients with an $\text{ALC} \leq 2050/\text{L}$, 33.6 % developed chronic ITP, while 22.4 % of those with an $\text{ALC} > 2050/\text{mm}^3$ followed a chronic course [OR 2.42, CI (1.37, 4.50)]. Ahmed et al. [7] reported that ALC cut-off value sensitivity was 69 %, specificity was 66 %, and PPV and NPV were 39 and 87 %, respectively. Our study demonstrated that ALC cut-off value sensitivity was 56 %, specificity was 76 %, and PPV and NPV were 55.2 and 66.9 %, respectively. In our study, a younger cutoff age of >6.75 years was observed in association with chronic ITP. Of the patients >6.75 years of age, 35.4 % developed chronic disease, while only 15.2 % of those aged ≤ 6.75 years had chronic ITP [OR 1.33, CI (0.91, 1.93)].

In conclusion, our study showed that ALC is a statistically strong predictor of developing chronic ITP in pediatric patients. Also, further prospective studies may explain the association of low lymphocyte counts at presentation and chronic ITP.

Compliance with Ethical Standards

Conflict of interest No financial and commercial conflict of interest.

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