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Original Article

Assessment of Clinical and Laboratory Predictors for Chronic Childhood Immune Thrombocytopenia

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ABSTRACT

Aim: To determine the risk factors associated with chronic childhood immune thrombocytopenia (ITP).

Materials and Methods: We retrospectively analyzed the medical records of 123 children with ITP who were admitted to our Department of Pediatric Hematology between May, 2006 and May, 2019. We evaluated their demographic, clinical, and laboratory characteristics, and assessed the risk factors associated with chronic ITP in childhood.

Results: Of the 123 children with ITP, 60.2% were male, with an average age of 6.4±4.0 years. At follow-up, 93 (75.6%) of the patients were diagnosed as acute ITP, whereas 30 (24.4%) progressed to chronic ITP with a platelet count of lower than 100×10^9/L at the end of the 12-month follow-up period. Older age at admission [Odds ratio (OR): 1.4, 95% confidence interval (CI): 1.2-1.6, p<0.001], female gender (OR: 4.1, 95% CI: 1.5-10.3, p=0.003), and insidious onset of the symptoms (OR: 5.0, 95% CI: 1.1-22.6, p=0.03) were determined to be risk factors for chronic ITP.

Conclusion: Our study indicates that older age, female gender and insidious onset of the disease at admission may predict chronic ITP in childhood.

Keywords: Immune thrombocytopenia, risk factors, children

Introduction

Childhood immune thrombocytopenia (ITP) is an immune-mediated disorder characterized by an isolated decrease in platelet levels (<100×10^9/L) in the absence of other causes of thrombocytopenia (1,2). The overall incidence of ITP in children under 18-years is reported to be 8.8 per 100,000 person-years (3). ITP is idiopathic in most cases, but some children may present following a viral infection or immunization (4,5). Clinical manifestations are related to the severity of thrombocytopenia and include purpura and also life-threatening bleeding episodes in rare cases.

Currently, the pharmacological treatment for ITP is recommended in children with significant bleeding regardless of platelet count (4,5). ITP typically has a benign course in childhood and most recover at 6-18 months after diagnosis. However, in 20-30% of patients, it progresses to chronic ITP, defined as the persistence of thrombocytopenia (<100×10^9/L) for more than 12 months (1,2).

Once diagnosed, those children with chronic ITP, and their families, often experience a range of physical and emotional difficulties while they try to cope with the fear of relapse of the disease.

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Chronic ITP may be associated with several pharmacological, laboratory, and genetic factors such as age, gender, onset type, previous vaccination or viral infection, platelet counts at admission, and treatment with IVIG and/or steroids (1,6-8). Determining the predictive factors for chronic disease may be beneficial for the patients, their parents and the treating physicians.Therefore, in this study, we aimed to identify those risk factors which predict childhood chronic ITP.

Materials and Methods

This was retrospective cohort study conducted at a single center of a tertiary hospital in Turkey, between May, 2006 and May, 2019. During the 13-year study period, a total of 123 children with newly diagnosed ITP, with a platelet count of $<100\times10^9$/L, who were followed up at the Department of Pediatric Hematology were included this study. Patients with secondary thrombocytopenia or without isolated thrombocytopenia, <12 months or >18 years of age, those with insufficient data on file, and those who did not continue their regular follow-up at the outpatient clinic of pediatric hematology were excluded from this study.

The diagnosis of primary ITP was defined through patient history, physical examination, and laboratory tests which revealed isolated thrombocytopenia without any other underlying causes (1). Disease onset was noted as abrupt (duration of clinical findings <14 days at presentation) or insidious (clinical findings for ≥14 days at admission) (1,2). Data on hemoglobin, mean platelet volume (MPV), and platelet distribution width (PDW) values obtained at the time of admission were recorded. The first-line therapy of ITP for children includes oral/IV standard-dose corticosteroids, a short course of high-dose steroids, and IVIG (5). Those patients whose platelet counts were below 20×10^9/L and/or with significant bleeding symptoms received an IVIG dose of 1 g/kg for 2 days. Oral steroid was given at a dose of 1-2 mg/kg/day for 30 days or as 4 mg/kg/day for 4 days, while high-dose IV methylprednisolone (15-30 mg/kg) was administered via 30-60 minute bolus infusion for 3 days. IVIG plus IV methylprednisolone was the definition of the combined strategy (5). A bone marrow aspiration was performed to rule out other causes of thrombocytopenia if the patients displayed unusual symptoms or had a poor response to IVIG. Additional tests such as autoimmune screenings were performed in those patients who were refractory to treatment.

After discharge, all patients were followed up at our outpatient clinics of pediatric hematology for at least for 12 months. Chronic ITP was defined as persisting thrombocytopenia of less than 100×10^9/L lasting for more than 12 months and persistent ITP referred to those patients who did not achieve spontaneous remission or did not respond fully to treatment for 3 to 12 months after diagnosis (9). Medical data on age at admission, gender, season, family history of ITP, history of antecedent infection (4 weeks before admission), or recent vaccination (3 months before diagnosis) (1,2,5) were recorded on previously prepared forms. Laboratory analyses, presenting symptoms, and therapy options (steroid, IVIG, or combination) were noted. The acute and chronic ITP groups were compared in terms of their demographic, clinical and laboratory characteristics. Then, possible risk factors for chronic ITP were determined.

This study received approval from the Ege University Medical Research Ethics Committee and was conducted in accordance with the 2013 Helsinki Declaration guidelines.

Statistical Analysis

SPSS software for Windows version 23.0 was used to analyze all the data (IBM, Armonk, NY: IBM Corp.). Descriptive statistics were used including mean (with standard deviations) and median (range: minimum-maximum) for continuous variables, and counts (percentages) for categorical variables. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Initially, Student's t-test and the Mann-Whitney U test were used to compare continuous variables for parametric and non-parametric variables, respectively. The chi-square test was used for categorical variables. Receiver operating characteristic (ROC) analysis was performed for the importance of age in the differentiation of acute and chronic ITP cases. Next, the risk factors for chronic ITP were analyzed using the stepwise method in multivariate logistic regression analysis. The independent variables included in the model were those that were found to be significant (≤0.01) in univariate analyses. Results from the regression are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All reported p-values are 2-sided. Statistical significance was set at p-values of less than 0.05.

Results

Of 123 patients, the female-to-male ratio was 0.66; 74 (60.2%) of the patients were male, and 49 (39.8%) were female. The mean age of the patients was 6.4±4.0 years (range; 1-15 years). According to ROC analysis, the area

under the curve was 0.840, sensitivity was 80%, specificity was 89.25% and the best cut-off point was determined to be 9 years of age. At admission, abnormal physical findings were identified in 111 (91.0%) of the patients; 12 (9%) children had a diagnosis of ITP based only on their laboratory results. Petechiae, ecchymosis, and purpura were detected in 95 patients (77.3%), while 28 (22.7%) had epistaxis and dental bleeding. At admission, presenting symptoms were present for longer than 2 weeks (insidious onset) in 22 of the patients (17.9%).Initially, the mean platelet count for all patients was 33.5±30.5×10^9/L, (range: 2-123×10^9/L), with a MPV of 8.9±1.6 fL (range: 0-20.2). Thirty-eight patients (30.9%) required bone marrow aspiration; and of these, 35 patients (92.1%) had increased megakaryocyte production. At follow-up, among the 123 patients, 93 (75.6%) were defined as acute ITP, while 30 (24.4%) progressed to chronic ITP with a platelet count of lower than 100×10^9/L at the end of the 12-month follow-up period. Although this study focused on newly diagnosed and chronic ITP patients, there were 25 cases that could be defined as persistent according to the data collected (platelet count below 100,000 at 6 months). All of these 25 patients were diagnosed as chronic ITP at the end of 1-year follow-up.

After the diagnosis of ITP, 92.7% of the patients received treatment (n=114), while 9 (7.3%) were followed up without any medication (i.e., wait-and-see approach). Among the treated patients, 85 (74.6%) were given IVIG, 22 (19.3%) had combined treatment (steroid + IVIG), and 7 (6.1%) had only steroid treatment.

Clinical course of the disease and risk factors for chronic ITP

In univariate analysis, the average age of those patients with acute ITP was lower than that of those with chronic ITP (5.0±2.9 vs. 10.7±3.7 years, p<0.001). Female patients had a higher prevalence of chronic ITP (40.8% vs. 13.5%, p=0.001). The rate of abrupt onset of symptoms was substantially higher in those individuals with acute ITP (95.2% vs. 18.6%, p=0.018). There were clinical signs in 11 (36.6%) of the 30 cases who developed chronic ITP.At admission, hemoglobin levels, platelet count, MPV, and PDW were similar in those patients with acute and chronic ITP. However, WBC count was higher in those patients with acute ITP (9.0±3.2 10^3/μL vs 7.7±2.7 10^3/μL) (p=0.027). Thirty patients (24.4%) underwent antinuclear antibody (ANA) testing, with a 43.3% (n=13) positivity rate. There was no significant difference in terms of ANA positivity between acute and chronic ITP (p=0.17). There was no significant difference regarding the type of treatment given at the time of diagnosis (p=0.111) (Table I). Four patients with chronic ITP required splenectomy. Splenectomy enabled full recovery in only one case; the others were still on combined treatment.

Chronic ITP risk factors were investigated by using logistic regression analysis. In the multivariate model, it was found that the risk of chronic ITP was greater with increasing age (OR: 1.4, 95% CI: 1.2-1.6, p<0.001). In the age-adjusted model, girls were at 4.1 times higher risk of chronic ITP (95% CI: 1.5-10.3, p=0.003) and insidious onset at admission was associated with the chronicity of the disease (OR: 5.0, 95% CI: 1.1-22.6, p=0.03) (Table II).

Table I. Comparison of the clinical and laboratory characteristics of patients with acute and chronic ITP

Variables	Acute ITP (n=93)	Chronic ITP (n=30)	p-value
Age at diagnosis (year)†	5.0±2.9	10.7±3.7	<0.001
Gender Female Male	 29 (59.2) 64 (86.5)	 20 (40.8) 10 (13.5)	 0.001
Family history of ITP‡	6 (6.4)	4 (13.3)	0.250
Antecedent infection‡	73 (78.4)	26 (86.6)	0.320
Recent vaccination‡	8 (8.6)	1 (3.3)	0.450
Abrupt onset‡	79 (95.2)	7 (18.6)	0.010
Season (Winter + spring)‡	60 (64.5)	24 (80.0)	0.110
Any clinical finding‡	83 (89.2)	29 (96.7)	0.290
Laboratory values			
Platelets ×10^9/L†	34.5±3.2	30.3±2.1	0.420
Hemoglobin (g/dL)†	10.8±1.3	11.3±1.3	0.080
WBC ×10^3/μL†	9.0±3.2	7.7±2.7	0.020
MPV (fl)†	8.8±1.8	9.0±1.2	0.430
PDW†	15.6±2.5	16.0±0.9	0.200
Type of treatment‡			
IVIG alone	66 (78.6)	19 (63.3)	0.210
Steroid	5 (6.0)	2 (6.7)	
IVIG plus steroid	13 (15.4)	9 (30.0)	

‡: n (%), †: mean ± standard deviation
ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulin G, MPV: Mean platelet value, PDW: Platelet distribution width, SD: Standard deviation, WBC: White blood cell

Table II. Logistic regression analysis results of the risk factors for chronic ITP among all study patients

	OR	95% CI	p-value
Age	1.4	1.2-1.6	<0.001
Gender Female (ref) vs. Male	4.1	1.5-10.3	0.003
Clinical findings Abrupt (<2 weeks) (ref) vs. Insidious (>2 weeks)	5.0	1.1-22.6	0.035
WBC count (at admission) <6.0x10^3/µL (ref) vs. ≥6.0x10^3/µL	2.5	0.7-8.5	0.120

CI: Confidence interval, ITP: Immune thrombocytopenia, WBC: White blood cell, OR: Odds ratio

Discussion

In this retrospective cohort study, we evaluated the predictive risk factors for chronic ITP among 123 children who were followed up at the Department of Pediatric Hematology of our hospital. Although the majority of children with ITP showed a full recovery, about 20-25% of the cases experienced persistent thrombocytopenia lasting longer than a year following diagnosis (8-10). Shaw et al. (3) investigated the incidence and clinical burden of ITP in children in the United States and reported that nearly one-third (32.4%) of cases with ITP appeared to be persistent (lasting 3-12 months); and 15.9% had evidence of chronic ITP (lasting >12 months) during follow-up. In another study, Alam (8) evaluated the records of 95 children between 0-15 years over a 10-year period and reported that only 5 (5.3%) developed chronic ITP. In the current study, 30 out of 123 patients (24.4%) had a diagnosis of chronic ITP. Due to the high impact of ITP on a child's everyday life, as well as being able to decide which treatment should be initiated, there is a critical need to predict the course of childhood ITP in order to guide the patients, the parents, and the treating physicians. Heitink-Pollé et al. (10) conducted a meta-analysis, reviewing and evaluating all clinical, laboratory, pharmacologic, and genetic determinants over the course of childhood ITP. They reported the predictive factors as being at an older age at the time of diagnosis, female gender, no history of infection or vaccination, insidious onset, higher platelet counts at presentation (>20×10^9/L), and positive ANA titers.

In a review on ITP, it was suggested that infants had a better chance of having a short duration of the disease, while adolescents had a higher risk of chronic disease (7). In the current study, similarly, we found that that the risk of chronic ITP was greater with increasing age (OR: 1.4, 95% CI: 1.2-1.6).

ElAlfy et al. (11) found that females more than 10 years of age were more susceptible than males in terms of following a chronic course. However, Yaprak et al. (12) studied a total of 350 children (186 females, 164 males) between the ages of 6 months and 16 years and did not find a gender predominance related to chronic ITP. In our study, the female gender was found to be a predictive factor for the development of chronic disease.

Some studies demonstrated significant associations with the absence of antecedent infection and the insidious onset of symptoms with the development of chronic ITP. Revel-Vilk et al. (13) found that a short course of ITP was associated with the presence of clinical symptoms 2 weeks prior to the disease and a younger age. Similar studies also demonstrated that the age at diagnosis, the duration of the clinical findings at diagnosis, and short-term recovery from ITP were powerful predictors (14-17). In our study, a longer duration of symptoms at diagnosis was a predictive factor for the development of chronic disease. We also evaluated the season in which patients showed their first symptoms, but no significant relation with chronic ITP was found, as was also stated in a meta-analysis (10).

In ITP, megakaryocytes produce platelets in response to an increased demand and newly generated platelets have a bigger size. Hence, platelet indices including MPV, PDW may provide vital information for megakaryopoietic activity in ITP (18,19). Tang et al. (18) showed that when the optimal cut-off points of MPV were equal to or larger than 9.35 fL, diagnosis of ITP had a sensitivity of 70.3% and a specificity of 74.8%. Chen et al. (20) found a non-linear connection between MPV and ITP relapse, with the inflection point being 21 fL. However, Söğüt et al. (16) reported that they observed no significant relationship between hematological parameters such as platelet, WBC, and MPV and the chronic course of ITP. In our study, similar to Söğüt et al.'s (16) study, there was no difference between patients with acute and chronic ITP in terms of the MPV value detected at admission (acute ITP: 8.8±1.8 fL, chronic ITP: 9.0±1.2 fL, p=0.43). WBC counts in both groups were within normal ranges (acute ITP: 9.0±3.2×10^3/µL, chronic ITP: 7.7±3.2×10^3/µL, 0.02), despite being greater in those patients with acute ITP. In further analysis, WBC count was not found to be a risk factor for chronic ITP.

In our country's and many international guidelines, steroids are recommended as the first-line treatment for patients with ITP who require pharmacological treatment. However, the 2019 American Society of Hematology guideline for children with ITP includes IVIG as a first-line

treatment in addition to steroids. The guideline states: "For children newly diagnosed with ITP with non-life-threatening mucosal bleeding and/or decreased health-related quality of life, the ASH Guideline Panel recommends anti-D immunoglobulin or IVIG". Treatment recommendations for ITP can be flexible according to guidelines and patient needs. Although steroid therapy predominates in clinical practice, IVIG can reduce the risk of progression to chronic ITP and favorably affect prognosis. It has been hypothesized that IVIG prevents the onset of chronic illness because of its long-lasting immunomodulatory effects, which include an increase in the quantity and functionality of regulatory T cells (21,22). Yacobovich et al. (7) also stated that IVIG therapy may alter the disease's clinical course by restoring the immunologic balance and activating regulatory T cells. In addition, IVIG acts relatively quickly, usually within a few days, to increase platelet counts in ITP patients. This can be particularly useful when the patient needs a rapid increase in platelet counts, such as during bleeding episodes or before surgery. Finally, steroids such as prednisone have several side effects when used long-term or at high doses, including weight gain, psychiatric symptoms, hyperglycemia, osteoporosis, and immunosuppression. In contrast, IVIG is generally well tolerated and has fewer systemic side effects (9). The more widespread use of IVIG treatment in our study may be due to these reasons.

In our research, 75.6% of the patients were defined as acute ITP, while the remaining 24.4% developed chronic ITP. Since the majority of our patients required treatment, we chose IVIG as the first line of treatment. We did not find any significant difference between the treatment type and progression to chronic ITP.

Secondary treatment options are used in those patients who do not respond to primary treatment. Rituximab may be used if there is no response to primary treatment (IVIG, anti-D, conventional dose steroid) and bleeding persists (level of evidence 2C). As in patients with chronic ITP, rituximab is recommended as an option for splenectomy or in patients who do not respond to splenectomy (level of evidence 2C). However, second step therapies such as rituximab and splenectomy are not without significant adverse effects (4). Splenectomy is performed if there is life-threatening bleeding which is unresponsive to treatment in acute ITP, or if there is a platelet count of $<30\times10^9$/L in chronic ITP at 12 months of follow-up. Splenectomy rates have been steadily decreasing over time with the increased use of pharmacologic therapies (23). As splenectomy may offer a high efficacy with a partial response rate of 83% and a complete response rate of 74%, the outcome and the associated risks cannot be predicted in a given patient (24). Consistent with this trend, only four patients in this cohort underwent splenectomy.

Traditional ITP treatment strategies have been based on reducing increased platelet destruction. However, in recent years, after cell culture studies showed that, contrary to expectations, increasing TPO levels in ITP patients was not sufficient, methods based on increasing platelet production have been added to the secondary treatment policy. Romiplostim and Eltrombopag increase platelet production by activating TPO. Romiplostim is used in doses of 1-10 µg/kg once a week as a subcutaneous injection. The response occurs in 1-4 weeks and is maintained as long as the drug is continued. Eltrombopag is used orally at 25, 50, and 75 mg/day doses. Its effect starts after the second week. Both drugs have similar effects in patients with or without splenectomy. Easily manageable side effects such as headache, fatigue, epistaxis, nosebleeds, and arthralgia may occur in 20% of patients on these drugs. However, the main adverse effects of TPO agonists are a 10% decrease in thrombocytopenia from baseline after discontinuation of the drug ("rebound" thrombocytopenia), an increase in reticulin fibers in the bone marrow, and thrombotic complications. Hepatic impairment may be observed in 13% of patients using Eltrombopag. Safety data on the long-term use of these drugs are not yet sufficient (25). Additionally, data on their use in children are very limited (26).

Study Limitations

Our study has some limitations. First of all, a relatively small number of patients at a single center from Turkey constitute the research population; therefore, care should be taken while generalizing these results. Secondly, our study is based on a review of medical records due its retrospective nature. Existing data regarding the pre-admission infection history, severity and duration of bleeding at admission, and the type of treatment were extracted from the patients' files. Of course, how they were recorded by the clinician affects the reliability of this data. Finally, the lack of data on the use of second-line therapies in the patients included in this study limits the ability to comment on the prognosis in ITP patients. The data used in our study were collected retrospectively. The treatment modalities used in ITP patients may vary according to the clinical conditions of the patients, the side effects of the drugs, the patients' and relatives' preferences, and the physicians' experiences and preferences. The reasons why second-line treatments were not preferred in our study may be the relatively mild clinical

course of the patients included in this study, concerns about the side effects and risks of secondary treatments, insufficient follow-up periods, the previous treatment experiences of the physicians, and complex insurance and reimbursement procedures.

Conclusion

In conclusion, older age at diagnosis, female gender, and insidious onset of symptoms were significantly associated with the development of chronic ITP in our patients. We determined that these three factors might guide pediatricians in clinical practice as predictive factors for the chronicity of ITP.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval no: 19-4.1T/17, date: 17.04.2019).

Informed Consent: The written informed consent could not be taken from the patients due to the retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.A., H.G., Design: S.A., H.G., Data Collection or Processing: S.A., H.G., Analysis or Interpretation: S.A., H.G., Literature Search: S.A., H.G., Writing: S.A., H.G.

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