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Factors Affecting Chronicity in Childhood Immune Thrombocytopenia

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OBJECTİVES: Immune thrombocytopenic purpura (ITP) is the most common cause of childhood acquired thrombocytopenia. Spontaneous recovery within one year is common in acute cases. Whereas intravenous immunoglobulin (IVIG), corticosteroids or anti Rh immunoglobulin (Anti-D) treatments are used to increase the platelet count rapidly in cases with high risk of bleeding or those with hemorrhage. We aimed to evaluate initial responses to various treatments in childhood ITP and factors affecting chronicity in a single center cohort of pediatric and adolescent ITP patients.

MATERIALS AND METHOD:
The study included 143 patients under the age of 18 who were followed-up with the diagnosis of ITP and who presented within initial 12 months of the disease within 18 years of duration. The initial treatment responses of acute ITP and the factors influencing chronicity were evaluated.

FINDINGS:
Of the 143 patients nine were lost the follow up, 81 patients (60,4%) exhibited resolution of thrombocytopenia within 12 months. The sex and mean age were not different between acute(aITP) and chronic(cITP) patients (p>0,05). But aITP was more frequent below two years old (p=0,027). Patients who had insidious onset, who didn't have antecedent history of infection had higher chronicity rates. Platelet count at diagnosis was higher in cITP group (p=0,037). The median platelet count in the patients with cITP was 13,000(1000-122,000), which was significantly higher than in acute cases 8000(1000-62000)/mm^3(p=0.037). Observation only, methylprednisolone(MP) and IVIG applied to aITP patients as initial therapies, and they had similar initial resolution/response rates (89,5%, 82,5%, 87,1% respectively)(p=0,811). Steroid and IVIG therapies provided response faster than observation only (p<0,05).

CONCLUSION:
There is higher risk of progression to chronicity from acute disease in patients with an insidious disease onset, not having history of previous infection, and higher platelet counts at diagnosis. Although the initial response rates to different treatment options in aITP were similar, responses to MP and IVIG were faster.

Key Words: *Itp, Childhood, Treatment, Chronicity*

INTRODUCTION

Immune thrombocytopenic purpura (ITP); which is characterized by low platelet count, spontaneous petechiae, purpura, ecchymosis and mucosal hemorrhage is the most common cause of childhood acquired thrombocytopenia[1]. Increased destruction of platelets through

various immune mechanisms and decreased production in the chronic process are reported to play role in the pathogenesis of ITP [2]. It is most common between the ages of 2-4 [3]. The anually incidence is 2-5 / 100.000[4, 5]. The most serious complication is intracranial hemorrhage(ICH), which is less than 1%. There is often a history of infection or vaccination within 1-4 weeks. Approximately 70-80% of the cases recover within 12 months after admission and are diagnosed as acute ITP (aITP). In the remaining 20-30% of cases, thrombocytopenia lasts more than 12 months and they are diagnosed as chronic ITP (cITP)[6]. Of the cases 2-10% are followed as severe ITP refractory to standart treatments [7, 8]. Although spontaneous recovery may be seen in acute cases, intravenous immunoglobulin (IVIG), corticosteroids or anti Rh immunoglobulin (Anti-D) treatments are used to increase the platelet count rapidly in cases who has high risk of fatal bleeding.
In this study we aimed to evaluate initial responses to various treatments in childhood ITP and factors affecting chronicity in a single center cohort of pediatric and adolescent ITP patients.

MATERIAL AND METHODS:
For the retrospective study, approval was obtained from Hacettepe University Faculty of Medicine Local Ethics Committee of Medical Research (HEK 08/109-12). The study included 143 patients under the age of 18 who were followed-up with the diagnosis of ITP and who presented within initial 12 months of the disease between January 1990 and March 2008 (18 years) in the Pediatric Hematology Unit of Hacettepe University Faculty of Medicine. The diagnosis of ITP was made after distinguishing other etiologies by history, physical examination, complete blood count and peripheral blood smear. The diagnosis was confirmed by bone marrow aspiration examination in appropriate patients.
The date of birth, gender, date of diagnosis and also presenting symptoms, physical examination findings, past infection and vaccine history (1-4 weeks ago) in the first application were recorded. If symptoms started within the last two weeks, it was defined as sudden onset; if started more than two weeks before it was defined an incidious onset [9]. Major hemorrhages (ICH, intranasal bleeding, macroscopic hematuria, diffuse mucosal hemorrhage in multiple sites, bleeding causing anemia) were recorded [10]. Results of tests performed during admission [platelet count, serum levels of anti-nuclear antibody (ANA), anti-deoksiribonucleic acid (anti-DNA)] were recorded.
The initial treatment responses of acute ITP and the factors influencing chronicity were evaluated. If patient didn't have any therapy this was named observation only. Methylprednisolone (MP) therapy was given as mega dose methylprednisolone (MDMP) 30 mg/kg/day 3 days + 20 mg/kg/day 4 days oral single dose or [11] standard dose (SDMP) 1-2 mg/kg/day. IVIG therapy was given as 1g/kg/day for 2 days in 17 patients, 1g /kg/day for 1 day in 5 patients, 400 mg /kg/day for 5 days in 5 patients and 800 mg /kg/day for 1-2 days in 5 patients by IV slow infusion. After initial treatment in acute phase, increase of platelet count ≥ 100.000/mm3 was recorded as complete initial response. If platelet count remained below 30.000/mm3 it was named unresponsive. Patients had remission within the first 12 months were referred to as aITP, and those who had thrombocytopenia for longer than 12 months were referred to as cITP [6]. The patients with acute and chronic course were compared in terms of age, gender, onset of complaints (sudden / insidious), history of infection, history of vaccination, referral platelet count and seropositivity of ANA.
Statistical analysis: The normality of the data was evaluated by the Shapiro–Wilk test and Kolmogorov-Simirnov test due to sample size. Mean, standard deviation, median, minimum and maximum values were used as descriptive statistics for quantitative data. For group comparisons Mann Whitney U test, Kruskal-Wallis (K-W) test and after K-W test Conover pairwise comparison method were used. Qualitative data were summarized by count and

percentage, Pearson chi-square, continuity corrected chi-square and Fisher's exact tests were used for comparisons. ROC analysis was performed to determine the best cut-off value and the AUC. In all analyses, significance level was considered to be 0.05. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for analysis.

RESULTS:

Treatment Response

For the patients who presented in the acute period (n=143), observation only (n = 21, 16.7%), steroid (MP) (n = 61, 48.4%), IVIG (n = 33, 26.2 %) or steroid + IVIG (n = 11, 8.7%) therapies were preferred as the first treatment approach (Table 1).

When the patients were evaluated in terms of their response to the initial treatment options as observation only, steroid (MP), IVIG or steroid+IVIG, achieved initial complete response rates were; 89.5%; 82.5%; 87.1%; 77,8% respectively (Table 1). When the observation only, steroid and IVIG groups were compared, the initial complete response rates were not different (p = 0.811). Steroid+IVIG group was not included in the statistical analysis because the number of patients were insufficient for the analyse. The median time to initial complete response was 43 (4-339) days with observation only, 7 (3-250) days with steroid, 6 (2-184) days with IVIG, 26 (2-195) days with IVIG plus steroid. Steroid and IVIG therapies provided response faster than observation only (p<0,05) (Figure 1).

Table 1: Distribution of initial treatments given to ITP patients presenting in acute period

Treatment	Frequency	Complete initial response	Response time (days) median (range)
Observation only	21 (16.7%)	17 (89.5%)	43 (4-339)
Steroid (MP)	61 (48.4%)	47 (82.5%)	7 (3-250)
İVİG	33 (26.2%)	27 (87.1%)	6 (2-184)
İVİG+steroid	11 (8.7%)	7 (77.8%)	26 (2-195)
		P=0.811	P< 0.05

Complete initial response: platelet count ≥100.000 after treatment; Response time: time to platelet count ≥100.000 after treatment.

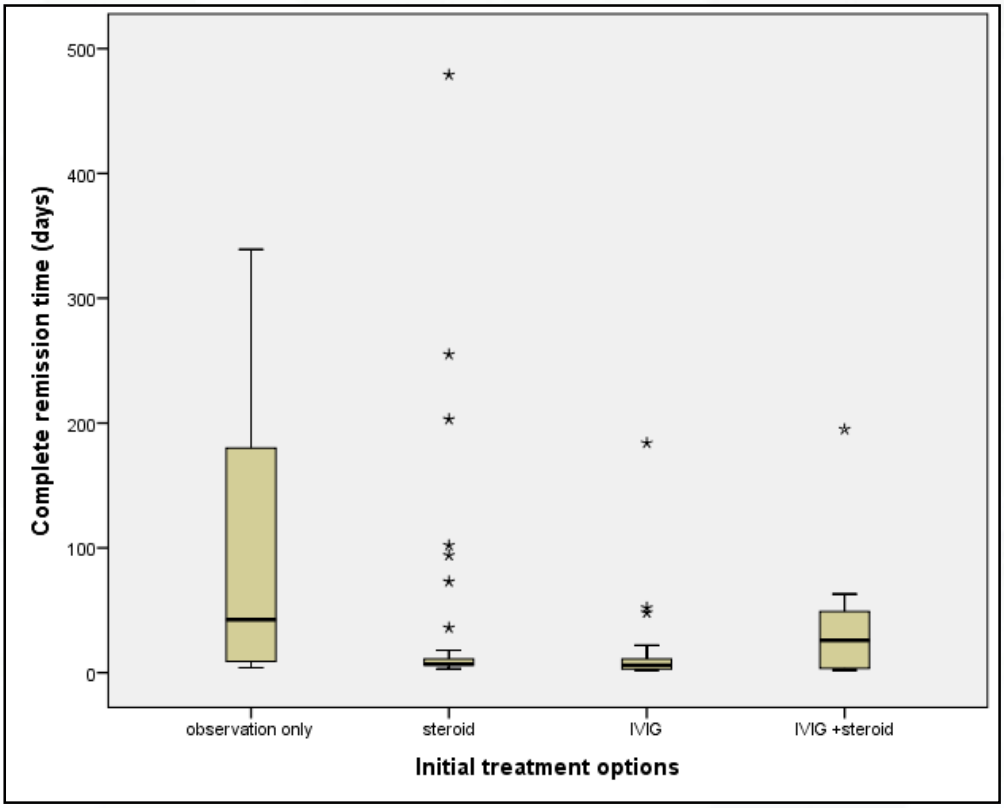

Figure 1: Complete initial response time after initial therapies.

Comparison of acute and chronic ITP cases

Of the patients (n=143), nine were lost the follow up, 81 (60,4%) had attained complete remission within the first 12 months and diagnosed as aITP, and 53 (39,5%) were diagnosed as cITP because their thrombocytopenia continued longer than 12 months. The mean age of aITP and cITP cases on first admission were 6.16 ± 4.0 (0,13-14,78) and 7.15 ± 3.63 (0,57-15,89) years, respectively (Table 2). The mean age of cITP patients was not significantly different than aITP patients (p>0,05). When the patients were grouped as under 2 years, 2-10 years and above 10 years of age, it was seen that the rate of acute cases was higher in the group under two years old than the other groups (p = 0,027) (Figure 2). There was no difference between the sexes in terms of chronicity (p = 0.87). Chronicity was significantly lower in patients with sudden initial complaints and those with a history of previous infection (p=0.00, p=0.004). There was no statistically significant difference between the patients with and without vaccine history (p = 0.527). The median platelet count in the patients with aITP was 8000 (1000-62000)/mm^3, which was significantly lower than in chronic cases 13,000 (1000-122,000) (p = 0.037) (Figure 2). When the patients were grouped as ≤ 20.000 / mm^3 and > 20.000 / mm^3 according to the platelet counts, chronicity was not different between groups (p = 0.148). Chronicity was not different between groups when the patients were divided according to platelet counts on first admission as <10.000/mm^3 and >10.000/mm^3 (p = 0.114). The cut-off point was 12.500 / mm^3 between the groups for the platelet count at diagnosis by ROC analysis (sensitivity 70.4%, selectivity 52%, AUC 0.609 ± 0.051). Acute ITP was more frequent in patients who has platelets below 12.500 /mm^3 at diagnosis(p=0,037). Of the patients who had positive ANA test, 8 (%66,7) had acute and 4 (33,3%) had chronic course and no statistically significant difference was found (p = 0.554).

Table 2. Comparison of clinical and laboratory features of patients with acute and chronic ITP

Features	Acute ITP (N = 81)	Chronic ITP (N = 53)	P
Age at diagnosis (years) Mean ± SD (Range)	6.16± 4.0 (0.13-14.78)	7.15±3.63 (0.57-15.89)	0.108
Age distribution (%)			
≤2 years	13 (92.9%)	1(7.1%)	
2-10 years	52 (55.3%)	42 (44.7%)	0.027
> 10 years	16 (61.5%)	10 (38.5%)	
Gender n (%)			1.0
Female	46 (60.5%)	30 (39.5%)	
Male	35 (60.3%)	23 (39.7%)	
Initiation of complaints n (%)			
Sudden	75 (71.4%)	30 (28.6%)	0.00
Insidious	6 (20.7%)	23 (79.3%)	
History of previous infection n (%)			
Yes	56 (71.8%)	22 (28.2%)	0.004
No	25 (45.5%)	30 (54.5%)	
Vaccination history n (%)			
Yes	8 (72.7%)	3 (27.3%)	0.527
No	73 (59.8%)	49 (40.2%)	
Platelet count on referral / mm^3			
median (range)	8000 (1000-62.000)	13.000 (1000-122.000)	0.037
≤20.000 / mm^3	64 (66.0%)	33 (34.0%)	0.148
> 20.000 / mm^3	17 (50%)	17 (50%)	
≤10.000 / mm^3	50 (68.5%)	23 (31.5%)	0.114
> 10.000 / mm^3	31 (53.4%)	27 (46.6%)	
≤12.500 / mm^3	57 (70.4%)	24 (29.6%)	0.018
> 12.500 / mm^3	24 (48.0%)	26 (52.0%)	
ANA positive n (%)			
Yes	8 (66.7%)	4 (33.3%)	0.554
No	53 (53%)	47 (47%)	

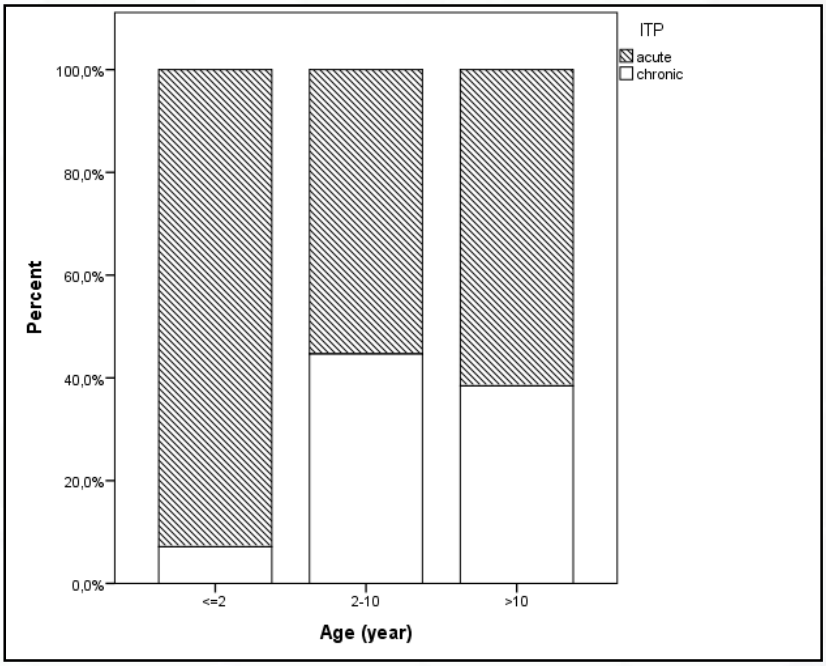

Figure 2: Distribution of childhood ITP according to age groups

Prognosis

Eighty-one (60,4%) of the cases underwent complete remission within the first 12 months. In a mean follow-up of 2.4 ± 2.9 (0.08-15.9) years, 102 (76,1%) patients (five after splenectomy) had complete remission, 19 patients' thrombocyte counts were stabilized above 30.000/mm^3, 13 (9,7%) had refractory thrombocytopenia. The most delayed remission occurred in the 177th month.

DISCUSSION:

The current approach in the follow-up and treatment of childhood ITP is the individual planning of the treatment according to the platelet count as well as the severity of the patient's bleeding, activity profile and compliance of the family with psychosocial issues [12]. In general, there is a consensus on shortening the risky period by giving medical treatment in cases who have life-threatening bleeding or significant mucosal bleeding. Treatment is still controversial in patients with mild symptoms like only cutaneous signs. Because the rate of remission without treatment is high, it is thought that mild symptoms can be observed without treatment by informing the family, but patients with a platelet count <10.000/mm3, head trauma, concomitant drug use that adversely affect platelet function are relieved of the risk of intracranial hemorrhage. IVIG is more preferred in the younger age group although there is no clear criteria for choice of corticosteroid or IVIG as the first choice when medical treatment is decided. Short-term MDMP treatment was widely accepted in our country because of its low cost, rare side effects and easy applicability. In addition, similar remission rates were observed MDMP versus IVIG treatments in several studies performed in our country. Özsoylu and colleagues randomized 20 patients to receive MDMP or IVIG, they found complete remission rates 60% in both groups on the third day of treatment and 80%, 90% on the seventh day of treatment. They indicated that the efficacy was similar in both groups [13]. Duru et al. suggested that MDMP and IVIG increased the platelet count more rapidly compared to non-treated monitoring, but they were not superior to the untreated monitoring in terms of remission rate [14]. In a current literature, 75 µg/kg anti-D has been reported to be effective in the treatment of aITP [15]. Although anti-D treatment is frequently used in cITP attacks, it can be used in aITP. In our study, there was no statistically significant difference in the rate of acute response between untreated observation, MP and IVIG

groups. It was observed that MP and IVIG treatments had an earlier response than observation only.

Treatment-related side effects were generally mild and transient. Aseptic meningitis occurred in three patients with IVIG as severe side effects and anaphylaxis in one patient.

Higher age at diagnosis (> 10 years), insidious onset, higher referral platelet count (> 10,000-20.000 / mm^3), no mucosal bleeding and no history of infection have been reported as risk factors for chronicity in childhood ITP in various publications [16-18]. It was reported that history of vaccination and treatment choice did not have an effect on chronicity and although the ratio of F/M was higher in cITP than in aITP the difference was not statistically significant [4]. In our study, the F/M ratio and mean age (years) at diagnosis were not different between groups. But in patients aged ≤ 2 years, aITP was more frequent. Chronicity rate was found to be higher in patients presenting with incidious complaints and patients without history of infection in our study. There was no statistically significant difference in the rate of chronicity among those who had a vaccination history or not. In our study, the median platelet count on referral was significantly higher in the chronic group ($p = 0.037$), and 12.500 / mm^3 is the cut off point, consistent with the literature.

Prognosis of childhood ITP is good and the remission rate is over 75%, almost 10% patients have refracter severe thrombocytopenia. When our patients were followed up for a mean of 2.4 years, the remission rate reached 76,1% in our study and the refractory ITP ratio was found to be 9,7%.

Conclusion

Although ITP, which is the most common acquired thrombocytopenia cause in childhood, is a benign disease, in our study 60,4% of the patients had remission in the first year and 9,8% of the cases had refractory ITP in the long-term follow-up. In the treatment of aITP, although similar initial response rates were obtained with observation only, MP or IVIG use; response to MP and IVIG was earlier. The age at diagnosis was not different between aITP and cITP. Presenting with incidious complaints, no history of previous infection, and higher platelet counts in first admission (above 12.500/mm3) were determined as risk factors for chronicity. Gender and vaccination history did not have any effect on chronicity. Because of cITP is more difficult to manage, clarifying the pathophysiological mechanisms for chronicity is needed and preventive treatment options should be developed.

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