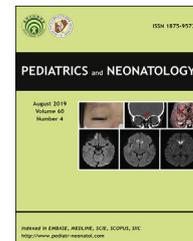




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Original Article

Retrospective evaluation of children with immune thrombocytopenic purpura and factors contributing to chronicity



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globulin

Abstract *Objective:* Immune thrombocytopenic purpura (ITP) is the most common cause of acquired thrombocytopenia children. The aim of this retrospective study is to describe presenting features and clinical characteristics of ITP and evaluate clinical course, treatment modalities, and complications and determine the effects of preceding infection history, age, gender, treatment modality, and admission platelet count on chronicity.

Method: Two hundred and eleven patients who were diagnosed ITP and followed-up in Department of Pediatric Hematology, Ankara Children Hematology Oncology Education and Research Hospital between January 2008 and September 2012 were included. Age of the patients, gender, date of admission, date of diagnosis, complaint in the application, previous infection and laboratory tests were recorded.

Results: Mean age of the patients on diagnosis was 5.4 ± 4.1 years. The female/male ratio was 1.03. The clinical courses were determined as acute or chronic in 72% and 28% of patients respectively. Mean age at diagnosis was significantly higher in chronic ITP ($p < 0.01$). Chronic course was significantly higher in female patients ($p < 0.05$). The most frequent complaint was bruises on the skin (68%). The most common physical examination findings were petechiae, purpura and ecchymosis (89%). Patients with a history of past infection (53.6%) and who had serologically positive infection (15.6%) frequently had acute course ($p < 0.01$). The most common serologically positive infection was *Rubella*. The mean platelet count was significantly

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higher in chronic ITP ($p < 0.01$). In the initial treatment of patients admitted in the acute phase, megadose methylprednisolone (MDMP) was used in 31% of patients, intravenous immune globulin (IVIg) in 55% of patients and anti-D in 2% of patients while 12% did not receive any treatment. There were no significant differences between the recurrence rate and treatment modality ($p > 0.05$).

Conclusion: In our study, in females and in patients without any history of past infection, platelet count $>20 \times 10^9/L$ and initial diagnosis age > 10 years were found to increase the probability of chronic disease, which is compatible with the literature.

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1. Introduction

Immune thrombocytopenic purpura (ITP) is the most common cause of acquired thrombocytopenia in childhood. It is characterized by thrombocytopenia with accelerated destruction mediated by antiplatelet antibodies and concomitant augmented production. Although its actual incidence is unknown, it is estimated to occur in 1/10000 children every year.¹ Forty to fifty percent of cases recover within the first month and seventy to eighty percent of cases improve in the first 6–12 months. The condition becomes chronic in 20–30% of children. In females and in patients without any history of past infection, platelet count $>20 \times 10^9/L$ and initial diagnosis age >10 years were found to increase the probability of chronic disease. Treatment of patients with ITP aims to maintain a high platelet count which is stable enough to prevent severe bleeding. Corticosteroids, intravenous immunoglobulin (IVIg) or anti-D immunoglobulin are used as first-line treatment.^{1,2}

The purpose of this retrospective study is to describe the clinical characteristics and to determine the factors that predict chronicity and response rate to first-line treatment and recurrence of the children with ITP.

2. Materials and methods

Three hundred children, who were followed-up with a diagnosis of ITP in Ankara Child Health and Diseases Hematology Oncology Education Research Hospital, Pediatric Hematology Department between January 2008 and September 2012, were evaluated retrospectively and the files of 211 patients with adequate information and follow-up duration were recruited into the study.

The diagnosis of ITP was established when the history, physical examination, complete blood count, and examination of the peripheral blood smear and/or bone marrow aspiration did not suggest other etiologies for the thrombocytopenia. The ages and gender of the patients, complaints at the referral and history of recent infection and vaccination (before 1–4 weeks) were recorded.

Complete blood count, Hepatitis B, Hepatitis C, *Toxoplasma*, Rubella, Cytomegalovirus (CMV), Epstein–Barr virus (EBV), Parvovirus, *Salmonella*, *Brucella*, antinuclear antibody (ANA), anti-dsDNA antibody, antiphospholipid

antibody (APL Ab), anticardiolipin antibody (ACL Ab), Coombs' test, C₃ complement, C₄ complement, Immunglobulin (Ig) A, Ig G and Ig M levels were recorded.

The patients who entered remission within 12 months were defined as acute ITP, while the ones who had thrombocytopenia lasting more than 12 months were defined as chronic ITP. The patients who did not respond to treatment or had a short and transient response to treatment were identified as refractory and those who developed thrombocytopenia after entering remission ≥ 3 months later were defined as recurrent ITP.^{3–5}

The patients with platelet count less than $20 \times 10^9/L$ and $\geq 20 \times 10^9/L$ with hemorrhage were treated. The treatment was defined as mega-dose methylprednisolone (MDMP) if methylprednisolone were used as 30 mg/kg/day for 3 days and 20 mg/kg/day for 4 days.⁶ IVIg was administered as 0.8–1 g/kg/day 1–2 days^{7,8} and anti-D treatment was given as 50–75 $\mu g/kg$ doses.⁹

After the treatment, the increment of platelet count up to $\geq 100 \times 10^9/L$ is defined as complete response (CR), platelet count of $<100 \times 10^9/L - \geq 20 \times 10^9/L$ is identified as partial response (PR) and platelet count of $<20 \times 10^9/L$ despite treatment is described as unresponsiveness.^{10,11}

Statistical analyses were performed using the Statistical Package for Social Science (SPSS), Version 18.0 (SPSS, Inc., Chicago, IL). Mean, median, interquartile range (IQR), minimum and maximum values and standard deviations were calculated for numerical parameters. Differences between acute and chronic groups were investigated by multi-chambered and (2 \times 2) chi-square test. Value of $p < 0.05$ was accepted as statistically significant difference.

The research was reviewed and approved by the training and research hospital ethics committee (2012–031).

3. Results

Of 211 patients, 104 patients were boys (49.3%) and 107 patients (50.7%) were girls. The mean age of patients at diagnosis was 5.4 ± 4.1 years. The most frequent complaints were bruising on the skin and epistaxis and other complaints were skin eruption, intra-oral bleeding, gingival bleeding, hemorrhage in the urine, increased menstrual bleeding and coincidental thrombocytopenia. The most common findings at the physical examination were petechia

and ecchymosis. Serious bleeding such as intracranial hemorrhage was not observed in any patient.

History of viral infections 1–4 weeks before the admission was noted in 53.6% of the patients ($n = 113$), 11 patients (5.2%) had a history of recent immunization and 33 patients (15.6%) had serologically positive infection. Nonspecific upper respiratory infection (42.7%) was the most commonly associated infection and *Rubella* was the most often identified specific infection (6.4%). The existence of ITP was mostly observed after measles, mumps and rubella (MMR) vaccine. Table 1 provides the characteristics of children at baseline.

ANA and anti-dsDNA titration was performed in 201 patients, ANA returning positive titers in 6.9% of the patients and anti-dsDNA returning positive titers in 3.4% of the patients. C_3 complement was low in 1.5% of the patients, C_4 complement was low in 2% of the patients and one patient was diagnosed with systemic lupus erythematosus.

IgA was low in 7.5% of the patients, IgG was low in 2.9% of the patients and IgM was low in 2.5% of the patients. Three patients were diagnosed with common variable immunodeficiency, three patients were diagnosed with transient hypogammaglobulinemia of infancy and one patient was diagnosed with selective IgA deficiency.

One hundred and fifty-one patients (71.6%) were diagnosed as acute ITP. However, sixty patients (28.4%) became

chronic during the follow-up period. The clinical presentation, laboratory findings and initial treatment of patients with acute or chronic ITP are presented in Table 2.

The mean age of acute ITP patients was 4.8 ± 3.9 years and 6.8 ± 4.2 years in chronic ITP patients. The mean age at the diagnosis was significantly higher in chronic ITP patients ($p = 0.001$). Thirty-five percent of girls and 21% of boys were diagnosed with chronic ITP. The chronicity in girls was significantly higher than in boys ($p = 0.015$). Thirty-nine of 98 patients (40%) without any history of previous infection became chronic pattern. Patients with a history of previous infection were found to have significantly lower chronic pattern ($p = 0.003$). The average platelet count in patients with acute ITP at the referral was $9.4 \pm 12.4 \times 10^9/L$, while it was $17.5 \pm 19.4 \times 10^9/L$ in chronic cases ($p < 0.001$).

At referral, MDMP was administered to 66 patients (31.3%), IVIG to 116 patients (55%) and anti D treatment to four (1.9%) patients. Observation only was preferred in 25 patients (11.8%). Forty-four patients (66.7%) receiving MDMP achieved a complete response; however, five of them (7.6%) were accepted as unresponsive. Complete response was present in 70 patients (60.3%) among the patients treated with IVIG, and four of them (3.5%) did not respond to the treatment. One of four patients receiving anti-D treatment achieved a complete response, while one patient did not respond. During the follow-up of 25 patients with watchful observation only, the platelet count was detected as $\geq 100 \times 10^9/L$ in 18 patients (72%). The type of treatment at referral and the treatment response rates are shown in Fig. 1.

Recurrence was observed in 37 patients (31.9%) who received IVIG, in 31 patients (46.9%) with MDMP, in 3 patients (75%) with anti D treatment and in 10 patients (40%) with observation only group. No significant differences were detected between treatment protocols ($p = 0.093$). The recurrence rates of initial treatment are demonstrated in Fig. 2. When the recurrence rates were compared, they were detected as significantly higher in patients receiving MDMP treatment rather than IVIG treatment ($p = 0.043$).

Chronicity was observed in 50 patients (26.9%) who received treatment and in 10 patients (40%) who did not receive treatment. The chronicity was significantly lower in patients under a treatment protocol ($p = 0.037$).

The average duration for responding to one of the treatment was estimated as follows: 5.4 days for MDMP (2–14 days), 3 days for IVIG (2–10 days) and 4.6 days for anti-D (2–7 days). There was no significant difference between MDMP, IVIG and anti D treatments in terms of average duration for responding to the treatment ($p = 0.413$).

4. Discussion

Immune thrombocytopenic purpura is a hematologic disorder characterized by low platelet counts due to immunologic destruction of normal platelets and suboptimal platelet production.^{12–16} ITP is observed in both genders with an equal frequency, and it is mostly detected in children aged from 2 to 6 years old.^{1,2}

As indicated in the literature, the most frequently reported symptoms at referral were cutaneous and mucosal

Table 1 Baseline characteristics of children diagnosed with immune thrombocytopenic purpura.

	n (%)
Female gender/female-male ratio	107 (50.7)/1.03
Acute ITP female gender	69 (45.7)
male gender	82 (54.3)
Chronic ITP female gender	38 (55.8)
male gender	22 (44.2)
Age	
<2 years	51 (24.2)
2–10 years	123 (58.3)
>10 years	37 (17.5)
History of viral infection	113 (53.6)
Serologically positive infection	33 (15.6)
Rubella	13 (6.2)
EBV	8 (3.8)
CMV	7 (3.3)
Toxoplasma	2 (0.9)
Parvovirus	2 (0.9)
Brucella	1 (0.5)
Hepatitis B	0
Hepatitis C	0
History of recent immunization	11 (5.2)
MMR vaccine	9 (4.3)
DPT vaccine	2 (0.9)
Type of medication initiated	
Corticosteroids	66 (31.3)
IVIG	116 (55)
Anti-D	4 (1.9)
Without treatment	25 (11.8)

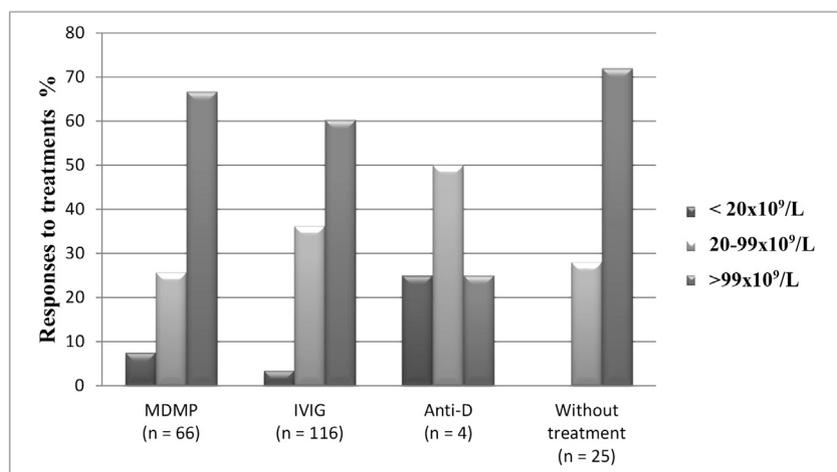
*DPT: Diphtheria-pertussis-tetanus vaccine *MMR: Measles, mumps and rubella vaccine.

*CMV: Cytomegalovirus *EBV: Epstein–Barr virus.

Table 2 Comparison of acute and chronic ITP patients (n = 211).

Features	Acute ITP (n = 151)	Chronic ITP (n = 60)	p value
Age at diagnosis (years) Mean ± SD	4.8 ± 3.9	6.8 ± 4.2	p = 0.001
	n (%)	n (%)	
<2 years	44 (86)	7 (14)	
2–10 years	87 (71)	36 (29)	
>10 years	20 (54)	17 (46)	
Gender	n (%)	n (%)	
Female	69 (65)	38 (35)	p = 0.015
Male	82 (79)	22 (21)	
Previous infection	n (%)	n (%)	
yes	92 (81)	21 (19)	p = 0.003
no	59 (60)	39 (40)	
Recent vaccination	n (%)	n (%)	
yes	10 (91)	1 (9)	p = 0.156
no	141 (71)	59 (29)	
Mean Hb (g/dl)	12.1 ± 1.4	12.5 ± 1.1	p = 0.017
Mean WBC(x10⁹/L)	9.6 ± 3.1	9.3 ± 3.1	p = 0.444
Platelet counts Mean ± SD	9.4 ± 12.4	17.5 ± 19.4	p = 0.000
	n (%)	n (%)	
≤20 × 10 ⁹ /L	131 (76)	41 (24)	p = 0.002
>20 × 10 ⁹ /L	20 (41)	19 (49)	
≤10 × 10 ⁹ /L	112 (77)	34 (23)	p = 0.011
>10 × 10 ⁹ /L	39 (60)	26 (40)	
Type of medication initiated	n (%)	n (%)	
MDMP	41 (62)	25 (38)	
IVIg	94 (81)	22 (19)	
Anti-D	1 (25)	3 (75)	
Without treatment	15 (60)	10 (40)	p = 0.037

*WBC: white blood cells; Hb: haemoglobin.

**Fig. 1** Initial treatment and response rates.

bleeding.^{2,10,12,14} About 70 percent of patients had a recent history of viral diseases or a vaccination history. The viral infections rate varied between 48% and 70%, and the most frequently reported infection was nonspecific upper respiratory infection.^{13,14,17,18} Fifty-four percent of our patients had a history of recent infections, mostly upper respiratory infection. Rajantie et al.¹⁹ reported that 6.9% of 506 patients with newly diagnosed ITP had a history of recent vaccination. Five percent of our cases had an immunization

history 1–4 weeks before the referral, and ITP was observed more commonly after MMR vaccines.

While there may be a viral infection history in patients with acute ITP, thrombocytopenia may be observed during the course of viral infections or soon after infection.²⁰ Seropositivity was detected in 16% of our patients against an infectious agent in the absence of any clinical symptoms.

Sixty-two percent of our patients entered remission within the first 6 months, while 10% of them achieved

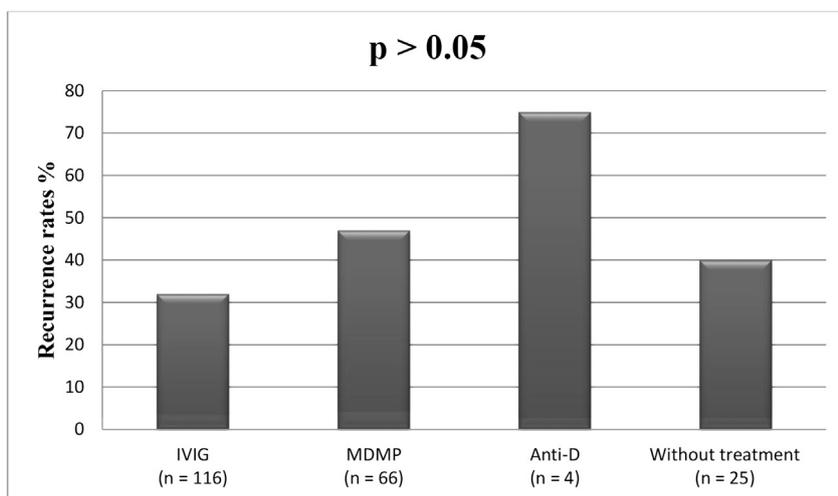


Fig. 2 Recurrence rates for initial treatments.

remission between 6 and 12 months. The findings were in accordance with the literature and supported the fact that ITP had a good prognosis in children.^{16,21,22} The remission rate within the first 6 months for childhood ITP was reported to be from 68 to 76%, and the chronicity was observed in 20–30% of cases, while 3–5% of patients demonstrated a recurrent course in acute ITP.^{3–5,10,12,14} Seventy-two percent of our patients had an acute pattern. Twenty-eight percent of our patients had a chronic pattern. The recurrence rate in acute ITP patients was 14%.

Diagnosis at over 10 years old, having a platelet count over $10\text{--}20 \times 10^9/\text{L}$, lack of mucosal bleeding, not having a history of viral infections and an initially positive ANA titer were the reported risk factors for chronicity.^{12,14,15} Although vaccine history and the treatment method did not have any effect on chronicity, the girl/boy rate was slightly higher in chronic ITP than in acute ITP.^{4,13–15} Female gender and higher age at diagnosis were identified as risk factors for the chronicity ($p < 0.05$, $p < 0.01$, respectively). Chronicity was detected more commonly in patients without any history of infections ($p < 0.01$). While there were no statistically significant differences between patients with or without a vaccine history ($p > 0.05$), chronicity in patients without any vaccine history tended to be higher. The average platelet count in chronic ITP patients at referral was estimated to be significantly higher than for acute ITP patients ($p < 0.01$).

The follow-up period and treatment of childhood ITP should be planned according to the platelet count as well as the severity of bleeding and family compliance. The general consensus is treating the case who has life-threatening bleeding or obvious mucosal bleeding.²³ Short-course MDMP treatment was a widely accepted treatment in our country due to its lower cost, rare side effects and easy applicability. Ancona et al.⁶ reported a statistically similar activity in two groups randomized in terms of MDMP and IVIG treatments. Duru et al.²⁴ compared MDMP, IVIG and watchful waiting and suggested that MDMP and IVIG increased the platelet count rapidly. Erduran et al.²⁵ reported that IVIG increased the platelet count up to $>20 \times 10^9/\text{L}$ in a short period; however, the remission rates were similar between groups.

In our study, first-line treatment options were MDMP, IVIG and anti-D and the following response rates were found: 92%, 97%, 75%, respectively. Twenty-five patients whose platelet counts were not decreased under $20 \times 10^9/\text{L}$ and no severe bleeding episode did not need any treatment. No significant differences were identified between mean duration of responses to MDMP, IVIG and anti-D treatments ($p > 0.05$).

Pharmacologic treatment at diagnosis was significantly associated with remission at both 12 and 24 months.²⁶ In our study, the chronicity was significantly lower in patients under a treatment protocol ($p < 0.05$).

Rosthoj et al.²⁷ reported the recurrence rate as 26% in cases receiving IVIG (1 g/kg/day, two days) and 40% in intravenous pulse methylprednisolone (30 mg/kg/day, two days). IVIG was reported to be superior in increasing platelet count; however, no differences were identified in terms of recurrence. In our study, the recurrence rate was identified as significantly higher in cases receiving MDMP ($p < 0.05$).

Finally, chronicity was greater among girls and cases without any history of infections, who had platelet count of $>20 \times 10^9/\text{L}$ at the referral, who were over 10 years old at the referral and who were receiving any treatment. Overall, ITP had a good prognosis, where male gender, younger age, and lower platelet counts predicted more favorable outcomes.

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Science (SPSS), Version 18.0 (SPSS, Inc., Chicago, IL). Mean, median, interquartile range (IQR), minimum and maximum values and standard deviations were calculated for numerical parameters. Differences between acute and chronic groups were investigated by multi-chambered and (2 x 2) chi-square test. Value of $p < 0.05$ was accepted as statistically significant difference.

Conflict of interest

The authors also declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pedneo.2018.10.002>.