ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 28(3): 477-483, 2023
DOI: 10.5505/ejm.2023.26675

Clinical Outcome of Childhood Immune Thrombocytopenia: Experience From A Single Tertiary Center In Turkey

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ABSTRACT

Immune Thrombocytopenic Purpura (ITP) is the most common hemorrhagic disease in children. Intracranial hemorrhage is the most severe complication requiring the administration of treatment for immune thrombocytopenic purpura. The present study aims to determine the clinical outcomes and factors affecting remission in childhood ITP.

The study included 503 children diagnosed with ITP in a Pediatric Hematology Polyclinic. Patient files and electronic registries were accessed retrospectively to obtain sociodemographic details, and diagnostic and therapeutic characteristics.

The mean age of the cases at the time of diagnosis was 6.18±4.30 years. Among all the cases, 446 (88.7%) were in remission. When the first treatments applied in cases with remission were evaluated, 190 (83.4%) patients had IVIG, 25 (56.8%) IVIG + pulse steroid, 34 (79%) pulse steroid, 7 (58%) IVIG + low dose steroid and 20 (83%) had low dose steroid treatment. Four cases developed intracranial hemorrhage during follow-up. The remission rate was significantly higher among the cases with low MPV (Mean platelet volume) values, high platelet counts and sedimentation values in the blood test at diagnosis ($p<0.05$). The responses to pulse steroids, low-dose steroids and IVIG for the initial treatment at diagnosis were similar, with none showing statistical superiority over any of the others ($p>0.05$).

This study features the largest single-center study in pediatric ITP. The frequency of remission was higher in the ITP-diagnosed cases who were male, who were diagnosed at a younger age, who had no epistaxis on admission, who had a history of URTI, and who had a high platelet count and sedimentation value and a lower MPV value at diagnosis.

Keywords: Children, immune thrombocytopenic purpura, treatment

Introduction

ITP is a common, acquired autoimmune disorder characterized by the presence of thrombocytopenia with a normal or increased megakaryocyte count in the bone marrow, increased antibodies and T-cell-mediated platelet damage, normal erythrocyte and leukocyte counts, and an absence of splenomegaly or other secondary thrombocytopenia causes (1). ITP is typically diagnosed between the ages of 1 and 9 years, and is most commonly seen in children aged 2–5 years within this age group. The incidence is 4–5.3 per 100,000 (2). Diagnosis is usually established based on history, physical examination, complete blood count and peripheral smear analysis. When bone marrow (BM) is examined, the megakaryocyte count is found normal or increased (3). The goal of treatment in childhood ITP is to prevent life-threatening conditions such as intracranial hemorrhage, which is rare as a complication, but of considerable concern. There may be spontaneous recovery in acute cases, however corticosteroid, intravenous immunoglobulin (IVIG) or anti-Rh immunoglobulin (Anti-D) therapies are used to rapidly elevate the platelet count in cases in which there is a high risk of fatal hemorrhage. If there is no response to these therapies in chronic cases, thrombopoietin receptor agonists, monoclonal antibodies (rituximab), immunosuppressive agents (azathioprine, cyclophosphamide, cyclosporine, vincristine), danazol or splenectomy may be suggested (4).

The present study makes a retrospective examination of patients diagnosed with ITP at our hospital, and establishes the clinical characteristics of patients and the efficacies of the selected treatments on admission.

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Received: 07.03.2023, **Accepted:** 01.04.2023

Materials and Method

The study included 503 patients aged 0–18 years who were diagnosed with ITP between January 1, 2013 and September 31, 2019 at the Van Dursun Odabaşı Medical Center Hospital. The study excluded patients with known previous chronic diseases, those on medication affecting liver and kidney function and platelet count/functions, and those who refused treatment. Patient files and electronic registries were accessed to record the age, gender, complaints, platelet count, season in which the diagnosis was established, treatments received, viral serological test results for etiology, rheumatological test results, history of previous infections and vaccination status. Acute ITP was diagnosed based on anamnesis, physical examination and laboratory analysis, and on the presence of isolated thrombocytopenia (platelet count <100,000/mm3) in a complete blood analysis, the absence of blasts in a peripheral blood smear and the lack of any indications of an underlying malignant condition (2). Thrombocytopenia detected in complete blood analysis was evaluated by a peripheral smear prepared by the finger stick method. The absence of pseudothrombocytopenia and other hematological causes was proven. An assessment of bone marrow aspiration was performed for newly diagnosed patients in the presence of a disorder other than thrombocytopenia detected in the blood count/peripheral smear analysis, or for cases with bone pain and unexplained organomegaly. Also assessed were patients with little or no response to first-line treatment (5). Acute ITP was considered for cases within the first 3 months of diagnosis, while persistent ITP was considered for cases within 3–12 months of diagnosis, those not in spontaneous remission or those who did not remain in remission once treatment was discontinued. Chronic ITP was defined as ITP lasting 12 months or more (2). The presence of a previous viral infection within the last month prior to diagnosis and the history of vaccination were considered as causative factors in the etiology.

Regarding treatment response, complete response was defined as a platelet count of >100x109/l, partial response as a platelet count of 30-100x109/l and a minimum of doubled initial platelet count, and non-response as a platelet count of <30x109/l and failure to reach a doubled initial platelet count (3,6). Rather than choosing a cause-driven treatment, the acute ITP was treated by increasing thrombocytopenia, which leads to or likely to lead to clinical signs, to a sufficient level that would not cause hemorrhage. Accordingly, the purpose of the treatment was to achieve a platelet level that ensures adequate hemostasis rather than reaching a normal platelet count (7, 8). The treatment regimes applied in our center for ITP include intravenous high-dose methylprednisolone ([HDMP] 30 mg/kg per day for 3 days and 20 mg/kg per day for 4 days), a standard dose of oral steroids (2 mg/kg per day for 14 days), intravenous immunoglobulin ([IVIG] 1 g/kg per day for 2 days), intravenous anti-D immunoglobulin (50 mg/kg per d for 6 days), and rituximab (375 mg/m2 per week for 4–6 weeks).

Statistical Analysis: Categorical data were presented as number and percentage; and continuous numerical variables as mean, standard deviation, median, minimum and maximum values. Categorical variables were compared using Pearson's Chi-Square test and Fisher's Exact test. A Shapiro-Wilk test and histogram were used to evaluate whether the numeric data were normally distributed. A Mann-Whitney U test was used for the pairwise comparison of non-normally distributed variables. The data were analyzed using SPSS 21.0 software, and a p value of <0.05 was considered statistically significant.

Results

The mean age of cases at diagnosis was 6.18±4.30 years. When examining the gender distribution of the cases, there were 263 (52.3%) male and 240 (47.7%) female patients. A seasonal admission examination showed that 153 (30.6%) presented in summer, 142 (28.4%) in winter, 125 (24.9%) in autumn and 83 (16.5%) in spring. Among our cases, 353 (70.1%) had acute ITP, 137 (27.3%) had chronic ITP and 13 (2.6%) had persistent ITP. During follow-up, 446 (88.7%) of all cases were in remission while 11.3% became chronic. At diagnosis, a history of Upper Respiratory Tract Infection (URTI) was detected in 148 (29.8%), and Acute Gastroenteritis (AGE) in 38 (7.6%) cases, while 16 (3.2%) presented for vaccination, and three cases each for bug bite, Lower Respiratory Tract Infection (LRTI) and chickenpox.

Upon physical examination, ecchymosis was identified in 273 (54.9%), epistaxis in 108 (21.7%), petechia in 101 (20.3%), gingival and oromucosal bleeding in 16 (3.2%), rectal bleeding in 10 (2%), and hematuria in seven (1.4%) (Table 1). The mean platelet value was 26.66±26.47, CRP value was 7.19±12.37, sedimentation value was

Table 1. Demographic, Anamnesis Characteristics and Accompanying Physical Examination Findings of Immune Thrombocytopenic Purpura Cases

Features	Number (n)	Percent (%)
Gender		
Male	263	52,3
Female	240	47,7
Presenting time (Season)		
Fall	125	24,8
Winter	142	28,2
Spring	83	16,5
Summer	153	30,7
Anamnesis features		
URI	148	29,8
AGE	38	7,6
Vaccination	16	3,2
Insect bite	3	0,6
Varicella	3	0,6
Symptom		
Ecchymosis	273	54,9
Epistaxis	108	21,7
Petechial rash	101	20,3
Gingival bleeding	16	3,2
Gastrointestinal hemorrhage	10	2,0
Menorragea	5	1,8*
Hematuria	7	1,4
Intracranial hemorrhage	4	0,8

AGE: Acute Gastroenteritis, ÜSYE: Upper Respiratory Infections

15.41±12.97, MPV value was 9.21±2.60 and PDW was 16.21±3.05 (Table 2). There was no blast infiltration detected in 167 (33.6%) cases with assessed bone marrow aspiration, although the megakaryocyte-series was increased, which was consistent with ITP. An etiological analysis of the cases revealed positivity for EBV in 126 (25.4%), parvovirus in 79 (15.9%), mycoplasma in 71 (14.3%), rubella in 21 (4.2%), HSV in 13 (2.6%) and CMV in four (0.8%). Viral serology was not studied in 200 (40.2%) of the cases. Among the cases that could be examined for autoimmune disorders, the celiac antibody was positive in 33 (6.6%), and ANA and anti-ds DNA were negative in 172 (88.9%), with positivity detected in two cases. The H. pylori antigen was found to be positive in 71 (14.3%) cases.

Remission was attained in 243 (92.7%) male and 208 (86.9%) female ITP cases. The rate of remission was significantly higher in the male than the female cases (p=0.034). Remission was achieved in 140 (94.6%) and 87.9% of cases with and without a history of URTI, respectively (p=0.024). Remission was significantly more frequent in cases with URTI at diagnosis or more recently. Remission was achieved in 16 patients with a history of vaccination, and all of the three patients with LRTI and chickenpox. Remission was attained in 91 (84.3%) and 355 (91.5%) of cases with and without epistaxis detected on physical examination at diagnosis, respectively. The rate of remission was significantly higher in the cases with no sign of epistaxis (p=0.027). It was established that the remission rate was unaffected by the presence of ecchymosis, petechia, gingival bleeding, rectal bleeding, menometrorrhagia, hematuria, hematemesis and cranial hemorrhage (p>0.05). The remission rate was significantly higher among the cases who were young in age at the time of diagnosis, and in those with a low MPV value, and high platelet count and sedimentation value (p<0.05). The remission rate was not affected by CRP, PDW, vitamin B12, anti-thyroglobulin or anti-TPO levels of the cases

Table 2. Diagnosis Age and Distribution of Some Blood Values İn Immune Thrombocytopenic Purpura Cases

Features	Medium	SS	Medyan	Minimum	Maximum
Age of diagnosis	6,18	4,30	5,25	0,30	17,33
Platelet ($x10^3$)	26,66	26,47	15,00	0,00	96,00
CRP	7,19	12,37	3,00	2,97	109,00
Sedimentation	15,41	12,97	11,00	2,00	82,00
MPV	9,21	2,60	8,90	5,00	30,00
PDW	16,21	3,05	16,80	1,10	30,00
Vitamin B12	340,59	139,55	309,00	157,00	978,00
Anti-troglobulin	12,65	20,47	3,46	0,00	140,75
Anti-TPO	21,91	66,57	2,17	0,00	487,06

CRP: C-reaktif protein, MPV: Mean platelet volume, PDW: Platelet distribution width, TPO: Tirozin peroksidaz

($p>0.05$). Of the total, four cases developed intracranial hemorrhage during follow-up. One was exitus, and two recovered with sequela and one without sequela.

Of the cases, 151 (30%) were followed-up without treatment. Table 3 presents the initial treatments after diagnosis. In an analysis of the response to initial treatment, pulse steroids, low-dose steroids and IVIG therapies were found to have similar response values ($p>0.05$). The response to IVIG+pulse steroid therapy was significantly lower than the pulse steroid monotherapy, low-dose steroids and IVIG therapies. Furthermore, the response to IVIG+standard-dose steroid therapy was significantly lower than IVIG therapy ($p=0.028$).

For the treatment of chronic ITP cases, low-dose steroid therapy was administered to 33 (6.6%) cases, IVIG+low-dose steroid therapy to 13 (2.6%), pulse steroid therapy to nine (1.8%), IVIG+low-dose steroid + Eltrombopag to nine (1.8%), IVIG therapy to seven (1.4%) and no therapy to 31 (6.2%). A splenectomy was carried out on 11 cases who were unresponsive to treatment.

Discussion

Immune thrombocytopenia (ITP) is a common hematologic disorder characterized by isolated thrombocytopenia. Spontaneous recovery from ITP occurs in approximately 80% of children, and usually within 6 months, but occasionally within one year or more (9, 10). Consistent with previous studies, our study found that the disease became chronic at a significantly higher level among women. A recent systematic review and meta-analysis study by Heitink-Polle et al. reported the female gender to be more prone to chronic ITP development (11). In line with literature, the analyses in the present study suggest that the frequency of remission decreases and the frequency of a chronic disease course increases with increasing age at diagnosis among ITP-diagnosed patients. The study by Donato et al. from Argentina evaluated 275 ITP cases and reported a high remission rate of 90% in babies and remission in 69% of older children. On the other hand, the authors indicated that only half of the adolescent cases attained remission, and suggested that this may be considered an indicator of poor prognosis when compared to younger children (12).

ITP prognosis and remission are affected by previous infectious diseases, and accompanying infections at diagnosis. Various infections prior to ITP diagnosis have been reported to be a common finding in childhood ITP. A large-scale, single-center study by Elfafy et al., conducted to determine the predictors of ITP, established a history of recent infection in more than half of the newly diagnosed, acute and persistent ITP cases, while an approximately one in four chronic ITP cases had a history of recent infection. The authors concluded that recent infections had a positive effect on prognosis of the disease (13). Smilarly, another study reported a positive impact of recent infections on prognosis (14). Viral agents that cause infectious diseases and that are common during childhood may result in a temporary immunological deregulation, leading to antiplatelet antibodies, which are potentially acute and self-limiting, and ITP. The "theory of molecular mimicry", which is suggested as a possible cause of this condition, is based on the temporary production of antiplatelet antibodies from the patient's lymphocytes due to similarities between the pathogen antigens and platelets. The antiplatelet antibodies produced attack the platelets of the patient within a limited time,

Table 3. Distribution of The Response Status According To The İnitial Treatment of Immune Thrombocytopenic Purpura

Features	Response		No response		Total		
	n	%*	n	%*	n	%**	p
Pulse steroid	34	79,1	9	20,9	43	8,6	0.026
Low dose steroid	20	83,3	4	16,7	24	4,8	0.027
IVIG	190	83,4	38	16,6	228	45,8	0.01
IVIG + Low dose steroid	7	58,3	5	42,7	12	2,4	
IVIG + Pulse steroid	25	56,8	19	43,2	44	8,8	
Anti-D	-	-	1	100,0	1	0,2	

* Row percentage is given
** Percentage of column is given

causing ITP manifestation. The occurrence of this condition "within a limited time" explains these findings (15). We believe that the increased erythrocyte sedimentation rate detected in our study occurred secondary to the previous infection, and therefore both the elevated sedimentation and previous URTI were more frequently associated with remission.

Platelet count at diagnosis is an important laboratory predictor of ITP course. With this in mind, in the present study we examined the initial platelet counts of the ITP cases and found significantly higher platelet counts among the patients who attained remission. The study by Lowe and Buchanan established the average platelet count at diagnosis as $21x10^9$/l in chronic ITP cases and $5.5x10^9$/l in newly diagnosed acute ITP cases. The authors thus reported a positive association between increased platelet count and chronic course development (16). Glanz et al. reported that an increased platelet count at diagnosis (>$20x10^9$/l) increased chronic course development by four times among cases over the age of 10. The authors further established that the same risk was 11 times greater at the cut-off point of platelets above $30x10^9$/l (17). Patients with ITP often experience mucocutaneous hemorrhage due to the reduction in the number of platelets, which is the most important component of hemostasis. To the best of our knowledge, literature contains no studies indicating a link between mucocutaneous hemorrhage and chronic disease course development. As an important difference that we did not encounter in any of the previously reported studies, our study was the first to establish a statistically significantly higher rate of remission among cases with no sign of epistaxis.

ITP may be seen as a side effect occurring following vaccination, and limiting the use of vaccine. ITP after vaccination is mainly reported in children after MMR immunization, although it is worth noting that ITP develops more frequently after measles, mumps and rubella infections than after MMR vaccination (18). Among our cases, 16 had a history of vaccination and attained complete remission. Previous studies have investigated the vaccination–ITP relationship, while the present study examines vaccination history, and identified no association between these two variables. Nevertheless, ITP incidence is substantially lower than natural diseases prevented by vaccination. For children with chronic ITP, it is recommended vaccination decision be made after assessing the benefit-to-harm ratio according to the measles risk within the population (19).

Given that ITP is an autoimmune bleeding disorder that presents with a binding of autoantibodies on the surface of platelets and then the destruction of platelets, various organisms may mimic the characteristics of human antigens and induce autoantibody production. Among such organisms is H. pylori. In a study analyzing stool samples of children diagnosed with ITP to evaluate the association between H. pylori infection and ITP prevalence in children, the ITP group was found to have a significantly different rate of stool HP-Ag antigens when compared to the healthy controls, and the authors recommended the administration of a urea breath test and stool HP antigen test for children with ITP (20). Our study found negative results in almost half of the cases undergoing an H. pylori antigen test, and established no significant link between remission attainment and the presence of H. pylori.

Our study examined the response status of ITP cases according to initial treatments. Among the research in this topic in literature, the study by Özsoylu reported a 90%-complete response rate by the end of 6 months with high-dose steroids (21). Buchanan et al. determined that the use of steroids (2 mg/kg/day for 14-21 days) was more effective than a placebo by the end of day 7 in their 27-case series (22). The 94 case series study by Imbach et al. reported a 77%-complete remission rate with the use of steroids (60 mg/m²/day for 21 days) (23). The study by Mazzucconi et al. of 61 cases achieved 83% complete response as a result of using steroids (1.5 mg/kg/day for 1 month, or until normal platelet levels were achieved) (24). In our study, 34 (79.1%) patients achieved complete response and nine (20.9%) patients had no response among the 43 ITP patients administered high-dose steroids during the initial treatment, while 20 (83.3%) had complete response and four (16.7%) were unresponsive among the 24 patients administered standard-dose steroids.

There have to date been only a limited number of studies evaluating the outcomes of a low-dose steroid + IVIG combination for ITP treatment. Gereige et al. divided 148 ITP patients into three groups who were administered respectively high-dose methylprednisolone, IVIG, and steroids + IVIG therapies. A comparison of the responses within the first 24 hours revealed combined therapy to be more effective, while IVIG was the least effective therapy (25). In our study, 23 (52.3%) of the 44 patients receiving pulse steroids + IVIG achieved complete response, while two (4.5%) achieved partial response and 19 (43.2%) were unresponsive. Additionally, six (50.0%) of the 12 patients receiving standard-dose steroid + IVIG achieved complete response, while one (8.3%) had partial response and five (42.7%) were unresponsive.

The study by Blanchete and Carcao reported that 2/3 cases attained spontaneous remission without the need for platelet-increasing treatment among children with acute ITP (26). The prospective study by Künhe et al. evaluated complete remission rates among patients being monitored without treatment, and those being administered IVIG and corticosteroid therapies, and reported a spontaneous remission rate of 68% among those being monitored without treatment (27). Similar to the studies in the literature, in the present study, remission was observed in 109 (72%) and no remission in 42 (28%) of the 151 patients under follow-up without treatment.

In conclusion, as seen in our study, the prognosis of childhood ITP is good. Our study is the largest single-center study among pediatric ITP studies conducted so far. In the first treatments given at the time of diagnosis, it was determined that there was a similar response in pulse steroid, low dose steroid and IVIG choices, and there was no statistically superiority to each other. Despite the development of major bleeding in some of our patients only one patient died. Steroids, which are more accessible, may be a good alternative for IVIG treatment because of the high cost of IVIG treatment and difficult accessibility.

Limitations: The study has a limited generalizability as it was conducted at a single center with the participation of patients who were under follow-up for a given period of time. The results of patients with missing data could not be assessed due to the retrospective design of the study. Specific analyses could not be made for the individual drugs, as the therapies administered to patients usually included multiple drugs. Due to the different dates of diagnosis, the time from diagnosis to study execution was different for each patient.

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