

Immune thrombocytopenia in children: An observational study in Tunisia

La thrombopénie immunitaire chez l'enfant: Une étude observationnelle en Tunisie

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ABSTRACT

Immune thrombocytopenic purpura (ITP) in children is a heterogeneous condition, varying in clinical features, need for treatment and outcome. Our study aimed to describe epidemiological, clinical and therapeutic data of ITP in our center. This study included patients aged between 2 and 18 years old, diagnosed with ITP during a 17-years period in the pediatric hematology department at Aziza Othmana hospital, in Tunisia. Thirty-one children were followed up for ITP during the study's period, with a mean age of 15 years old [2-18]. Eighteen patients (58%) had mild bleeding while 4 patients (13%) had severe hemorrhage. Buchanan score was higher than 2 in 12 patients (39%). The median platelet count was 14 G/L [1-85]. No etiology was identified in any of them. Eighteen patients were treated by oral corticosteroids (1mg/kg), 2 by intravenous corticosteroids and 4 by oral corticosteroids (4 mg/kg) in association with intravenous immunoglobulins. The rest of patients, were not in indication for medical treatment. Among the treated patients, 63% had a complete response, 29% a partial response and 8% were cortico-resistant. Seven patients were corticosteroid- dependent. Twelve patients relapsed (46%) with a median delay of relapse of 31 months [11- 106]. As a second line treatment, 10 patients were treated by corticosteroids (1 mg/kg), just one patient had a splenectomy. Management of ITP in children, represents a real challenge. Although corticosteroids and immunoglobulin are effective as first line therapy, the high rate of relapse highlights the need to improve new therapeutic strategies for second-line treatment.

Keywords: Immune Thrombocytopenic Purpura, Children, treatment.

RÉSUMÉ

Le purpura thrombocytopénique immunitaire (PTI) chez l'enfant est une affection hétérogène, variant en caractéristiques cliniques, besoins en traitement et résultats de résultats. Notre étude visait à décrire les données épidémiologiques, cliniques et thérapeutiques sur les PTI dans notre centre. Cette étude incluait des patients âgés de 2 à 18 ans, diagnostiqués avec une PIT pendant une période de 17 ans au service d'hématologie pédiatrique de l'hôpital Aziza Othmana, en Tunisie. Trente et un enfants ont été suivis pour une PIT pendant la période de l'étude, avec un âge moyen de 15 ans [2-18]. Dix-huit patients (58 %) ont eu des saignements légers tandis que 4 patients (22 %) ont eu une hémorragie sévère. Le score de Buchanan était supérieur à 2 sur 12 patients (55 %). Le nombre médian de plaquettes était de 14 G/L [1-85]. Aucune étiologie n'a été identifiée dans aucun d'eux. Dix-huit patients ont été traités par corticostéroïdes oraux (1 mg/kg), 2 par corticostéroïdes intraveineux et 4 par des corticostéroïdes oraux (4 mg/kg) en association avec des immunoglobulines intraveineuses. Le reste des patients n'était pas en indication pour un traitement médical. Parmi les patients traités, 63 % avaient une réponse complète, 29 % une réponse partielle et 8 % étaient résistants au cortico. Sept patients étaient dépendants des corticostéroïdes. Douze patients ont rechuté (46 %) avec un délai médian de rechute de 31 mois [11-106]. En traitement de seconde ligne, 10 patients ont été traités par corticostéroïdes (1 mg/kg), un seul patient ayant subi une splénectomie. La prise en charge de la PTI chez les enfants représente un véritable défi. Bien que les corticostéroïdes et les immunoglobulines soient efficaces comme thérapie de première intention, le taux élevé de rechute souligne la nécessité d'améliorer de nouvelles stratégies thérapeutiques pour un traitement de seconde ligne.

Mots clés: Purpura thrombocytopénique immunitaire, enfants, leucémie aiguë, traitement.

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) is a common disorder in children, with an annual incidence of 1.9–6.4 per 100,000 children. It is characterized by an isolated thrombocytopenia (platelet count < 100G/L), which occurs in most cases without a clear cause[1–3]. Based on its duration, newly diagnosed ITP indicating acute ITP within 3 months from onset, persistent ITP indicating an ITP lasting between 3 and 12 months and chronic ITP indicating ITP lasting more than 12 months[4]. Although it is a benign condition, with a favorable outcome, life-threatening bleeding may occur (gastro-intestinal, mucosal or intracranial) [2,5] which highlights the importance of an effective management of the disease. Treatment of ITP varies according to the importance of the thrombocytopenia and clinical manifestations. This study aims to describe epidemiological, clinical and therapeutic data of ITP in our center.

METHODS

This was a retrospective, monocentric study, carried out at the pediatric hematology department at Aziza Othmana hospital, in Tunisia. Children and adolescents aged between 2 and 18 years old, with a peripheral thrombocytopenia, monitored during the period from January 2016 to June 2023, were included. The following data were collected from the patients' medical records: sex, age, medical personal history, clinical features, blood cell counts, etiological investigations, first and second line treatment and response to treatment.

A meticulous clinical examination was performed in search of any lymphadenopathy, splenomegaly or associated signs and to evaluate the bleeding. The severity of bleeding was assessed according to Buchanan score [6].

Peripheral blood smear was reviewed in order to exclude a false thrombocytopenia. ITP was defined by a verified peripheral platelet count less than 100G/L. Bone marrow aspiration was indicated in case of presence of fever or tumoral manifestations, the presence of another cytopenia or if a corticotherapy was required (severe or life-threatening bleeding and/or platelet count < 10G/L). In order to exclude a secondary ITP, various investigations were performed. In first line, these investigations included: hemostasis evaluation, immunological assessments (Antinuclear antibodies, a weight immunoglobulin dosage and serum protein electrophoresis) and screening for hepatitis B, C, HIV, EBV, CMV and helicobacter pylori. A primary ITP was defined by the absence of an identifiable cause. If the thrombocytopenia was refractory for more than 3 months, additional tests seems necessary: Von willebrand factor antigen, ristocetin cofactor activity, factor VIII, and flow cytometry if Bernard Soulier is suspected.

Children was treated according to the recommendations suggested by the Tunisian Hematology Society[7]. Treatment was indicated in case of a platelet count less than 10G/L or the presence of at least a moderate bleeding

(Buchanan score= 3). Medical strategies varies from oral corticosteroids at the dose of 1 mg/kg or at the dose of 4 mg/kg during 4 days associated to immunoglobulins (0, 8 mg/kg), in the absence of a response. In case of severe or life threatening hemorrhage (Buchanan score= 4 or 5), patients required a hospitalization, platelet transfusions, intravenous corticotherapy and the administration of immunoglobulins.

A complete response was defined by a platelet count $\geq$ 100 G/L with absence of any bleeding, a partial response by a platelet count between 30 and 100G/L with at least 2-fold increase the baseline count and absence of bleeding. A platelet count < 30G/L or less than 2-fold increase of baseline platelet count or bleeding indicate the failure of treatment[8].

Corticosteroid-dependence was defined by the need for maintaining doses administration of corticosteroids for at least 2 months to keep a platelet count $\geq$ 30 G/L. Corticosteroid- dependent patients are considered as non-responders[8].

Patients who did not respond to first-line agents had additional courses of first-line agents.

In addition to specific treatment, supportive treatment was considered in some circumstances.

Platelet transfusions were indicated in life-threatening bleeding. Tranexamic acid was indicated in mucosal surface bleeding. Tranexamic acid was associated to contraceptive pills in case of menorrhagia. Emergency splenectomy may be considered in severe thrombocytopenia with life-threatening bleeding.

We then studied the different prognostic factors of chronicity: age >10 years, female gender, absence of recent vaccine or infection and platelet count > 20G/L[4], using chi square or Fisher test.

RESULTS

Thirty-one patients were collected. The median age was 15 years-old [2-18] (Figure 1), with a gender ratio (M/F) of 0.55. Five patients (16%) had a recent upper respiratory tract infection before the onset of the thrombocytopenia. No other infection or recent vaccination has been reported.

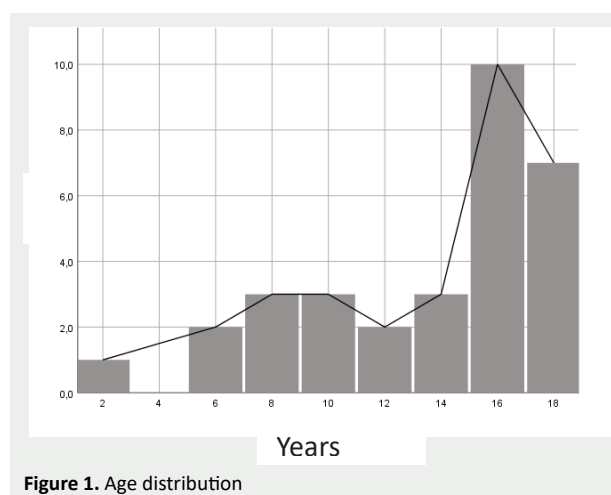


Figure 1. Age distribution

Nine patients (29%) were asymptomatic, and thrombocytopenia was discovered in a routine blood test. In the other 22 patients with bleeding: cutaneous bleeding (bruises and petechiae) was found in all of them, 10 of them (32%) had a gum bleeding, two (6%) had epistaxis and 3 girls reported menorrhagia. Four patients (13%) had a severe or life-threatening bleeding according to Buchanan score: 3 with oropharyngeal blood blisters and one with an intracranial bleeding at diagnosis. Different bleeding manifestations and distribution according to Buchanan score are summarized in table 2 and figure 2.

Table 2. Bleeding manifestations in patients with Immune thrombocytopenic purpura

Bleeding	Number of patients (%)
Cutaneous bleeding:	22 (71%)
Bruises	16 (52%)
Petechiae	14 (45%)
Gum bleeding	10 (32%)
Epistaxis	2 (6%)
Menorrhagia	3 (10%)
Oropharyngeal blood blisters	3 (10%)
Intracranial bleeding	1 (3%)

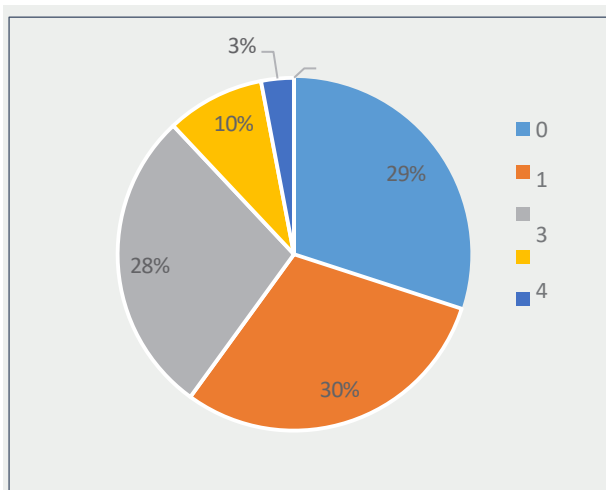


Figure 2. Buchanan score

The median platelet count at the onset of the disease was 14 G/L [1-85]. Twelve patients had a platelet count ≤ 10 G/L (39%), including the 4 patients with severe or life threatening bleeding. This association was statistically significant ($p=0.013$). Six patients (19%) had an associated microcytic anemia. Peripheral blood smear was done for all the patient, and it excluded the presence of macroplatelets or platelet clots. Bone marrow aspiration was done in 28 patients (90%) showing the presence of megakaryocytes, which confirms the peripheral mechanism of thrombocytopenia. All the patients were diagnosed as primary ITP.

Different first-line therapeutic strategies were summarized in figure 3. Intravenous corticotherapy was indicated in 2 patients (the one with intracranial bleeding and one with important oral blood blisters).

Platelet transfusion was indicated in the patient with intracranial hemorrhage. Tranexamic acid was prescribed in the 15 patients with mucosal bleeding. Contraceptive

pills were indicated, in addition, in the three girls with menorrhagia.

Four among the 7 non treated developed bleeding signs during their clinical course, requiring medical treatment, while the rest achieved spontaneous remission.

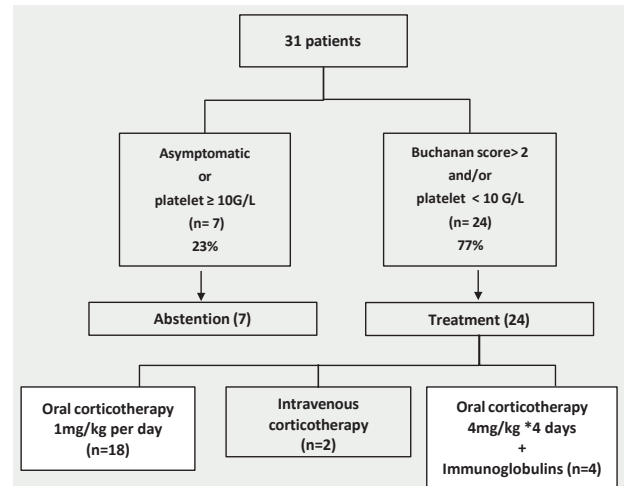


Figure 3. First line treatment

Among treated patients, a complete response was observed in 15 patients (63%) after a median duration of 1 month [1-4], while seven patients (29%) had a partial response. Two patients (8%) were corticosteroids-resistant. Seven patients (29%) were corticosteroids-dependant. The median duration of corticotherapy at the entire dose was 5 weeks [1-7].

Five patients, among the 22 patients with a complete or partial response, 5 patients relapsed after a median duration of 31 months [11-106]. ITP was persistent or chronic in 17 patients (55%). Ten patients were then treated by corticosteroids at the dose of 1mg/kg, and one patient had a splenectomy. The rest were under observation.

In our study, the prognostic factors of chronicity (age, female sex, recent infection, platelet count > 20 G/L) were not significantly associated with the evolution to chronic form (table 3).

Table 3. Prognostic factors of chronic Immune thrombocytopenic purpura

Prognostic factors	n	Non chronic ITP	Chronic ITP	p
Age > 10 years	22	11	11	1
Female gender	20	9	11	0.8
Recent infection	5	1	4	0.44
Platelet count > 20G/L	12	4	8	0.36

DISCUSSION

The present study provides an overview of the clinical characteristics and outcomes of pediatric ITP in our center. Most patients presented with cutaneous or mucosal bleeding. Severe bleeding manifestations were not common. Although the majority had a good response to first-line corticosteroid therapy, more than

half eventually developed a persistent or chronic disease, with no significant predictive factors identified.

ITP is a benign condition characterized by an isolated thrombocytopenia. It represents a common disorder in children, with a favorable outcome. However, severe bleeding may occur, threatening the life of the child[1–3,5]. Treatment is indicated in at least severe bleeding or in profound thrombocytopenia $<10\text{G/L}$. Therapeutic strategies vary depending on the clinical and biological features of patients and on the practices of each healthcare center[9]. ITP is mostly seen in children aged less than 10 years old, with a peak between 2 and 5 years old[9,10]. The age distribution in our study is quite different, most patients are aged between 16 and 18 years old. There is no gender difference in children with ITP in the different studies in the literature [9–11], though, we note a feminine predominance in our group of patients. A recent respiratory tract infection was reported in 6% of our patients, while its frequency varied between 24% and 60% in other studies[12–14].

In our study, most of the patients had no or mild bleeding, which is consistent with findings with other studies[5,13,14]. Severe or life threatening bleeding was found in 13% of the patients. This percentage is higher than reported in literature: in fact, the frequency of severe bleeding in different studies does not exceed 4%[3,15]. The median platelet count in our group of patients was 14 G/L . The four patients who had severe and life threatening at presentation had a platelet count $\leq 10\text{G/L}$ with a statistically significant association. This was consistent with the data reported by Kühne et al. and Neunert et al. [5,9]. Neunert et al. found that the mean platelet count in mild, moderate or severe bleeding was respectively 17G/L , 10G/L and 9G/L . This difference of the mean of platelet count according to the severity of bleeding was significant.

Bone marrow aspiration is not systematically required according to different guidelines: in fact it is only recommended if the patient presented other clinical feature (Bone pain, lymphadenopathy or enlarged spleen) or an associated abnormality in the cell blood count or if a treatment by corticosteroids is indicated[2,3,10]. Based on these recommendations, Lee and al. reported that 3 out of 52 children with ITP, in Children's Haematology and Cancer Centre in Singapore, had a bone marrow aspiration[1]. Similarly, Le Meignen et al. reported that 84.4% of the patients of their study did not have a bone marrow aspiration[12]. Choulout et al. explained the decrease of the percentage of patients who had a bone marrow aspiration after 1983, by the introduction of immunoglobulins in the treatment of ITP[13]. However, in our study, 90% of the children had a bone marrow aspiration. This huge difference may be explained by the fact that most of our children are treated by corticosteroids in first line, as immunoglobulins are not easily provided. Another Tunisian study conducted in a different center, including 140 patient, found a similar result (86%)[14].

Despite the different guidelines made to facilitate the management of ITP, treating children with ITP remains non-consensual, and depends on different factors[10,11].

Comparative to adults with ITP, children present more spontaneous remission within 6 months (70% versus 45% according to schifferli et al.)[16]. Besides, they have fewer comorbidity and a lower severe bleeding risk. Thus, unlike adults for whom a treatment is recommended when platelet count is below 30G/L , careful observation is the preferred management approach[15,16]. A dutch study by Heitink-pollé et al. proved that there is no difference in the rate of remission at 6 and 12 months from diagnosis, between using intravenous immunoglobulines (IVIG) or opting for active observation. Yet, a decrease in severe bleeding was observed in patients with moderate bleeding who received IVIG[17]. According to American Hematology society's (ASH) Guidelines of 2019[18], treating children with ITP depends on the severity of bleeding, the severity of thrombocytopenia and quality of life issues. In patients with no or mild bleeding and with a platelet count $> 10\text{G/L}$, observation is recommended. In children with no life-threatening bleeding, ASH recommends prednisolone at the dose of $2\text{-}4\text{mg/kg}$ for a period of 5 to 7 days rather than intravenous (IV) corticosteroids or immunoglobulins. In fact, prednisolone has an approximate rate of response of 75% in 2-7 days, which is similar to that obtained with IVIG with less immediate side effects. But the response to IVIG is more rapid (1-2 days)[2,3]. Hospitalization with administration of IV corticosteroids, immunoglobulins and platelet transfusion are reserved for patients with severe and life threatening bleeding or in case a faster raise of platelet count is desired[15].

In our study, abstention was opted for 23% of cases. Most of treated people had prednisolone at the dose of 1mg/kg for a median duration of 5 weeks before degression with a rate of complete response of 63% in a median period of 1 month. This therapeutic strategy was likely adopted by a Tunisian study by sfaihi et al., with comparable results[14]. Contrary to the French study by le meignen et al., patients were treated in first line by IGIV with a good response in 74% of patients in 36 to 48h[12].

Persistent or chronic ITP was observed in 58% of the patients of our study, was higher than the rate reported in the different studies in the literature[12,14]. In fact, although patients had a good response to treatment, relapse frequently occurred. This high rate may be explained by the predominance of patients aged more than 10 years in our group of study, which seems to be a risk factor for chronic ITP, according to Meignen et al[12]. For second line treatment, ASH 2019 recommends Thrombopoietin Receptor Agonist (TPO-RAs) rather than rituximab and splenectomy [18]. In our center, patients with persistent or chronic ITP were treated by oral corticosteroids. Splenectomy was performed in one patient with refractory disease. As for the TPO-RAs, this molecule couldn't be prescribed in our patients due to the absence of an adequate social healthcare coverage.

CONCLUSION

ITP is a frequent, benign condition in children, with generally a favorable outcome. However, its management

represents a significant therapeutic challenge. Although good response is usually obtained with corticosteroids, frequent relapse may occur, altering the life-quality of children. Thus, access to new therapeutic strategies as second line treatment is essential.

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