ORIGINAL ARTICLE

Chronic immune thrombocytopenic purpura in children: Clinical presentations and management

Purpura thrombopénique immunologique chronique de l'enfant: Présentations cliniques et prise en charge

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Abstract

Objective: the aim of this study is to report epidemiological data, clinical presentations and management of chronic immune thrombocytopenic purpura (ITP) in a single center in south of TUNISIA.
Methods: retrospective study collecting all cases of chronic ITP among children aged less than 14 years, in a department of pediatrics in south of Tunisia during a period of 13 years (from 1st January 2010 to 31 December 2022)
Results: during the study period, 72 newly diagnosed ITP were recorded; 11 patients evolves chronic ITP (12 ,5%). They were 6 boys and 5 girls. Two patients were aged more than 10 years at the onset of the disease. Symptoms in the chronic stage were mucocutaneous bleeding. One patient developed post traumatic cerebral hemorragia. Three patients had severe form, and required second-line therapy. Two patients requested Eltrombopag with good response.
One patient had spontaneous recovery after 3 years of follow up.
Conclusion: Management of chronic ITP represents a real challenge for pediatrician. Currently, there are some recommendations and guidelines which can guide management strategy of severe forms of Chronic ITP.

Key words: chronic immune thrombocytopenic purpura ; children; management

Résumé

Objectif: Le but de cette étude était de rapporter les données épidémiologiques, les présentations cliniques et les modalités de prise en charge du purpura thrombopénique immunologique (PTI) chronique dans un service de pédiatrie au sud Tunisien.
Méthodes: Étude rétrospective collectant tous les cas de PTI chronique chez les enfants âgés de moins de 14 ans, dans un service de pédiatrie du sud Tunisien sur une période de 13 ans (allant du 1er janvier 2010 au 31 décembre 2022)
Résultats: Au cours de la période d'étude, 72 patients ayant un PTI aigu ont été colligés ; dont 11 ont évolué vers la chronicité (12,5%). Il s'agissait de 6 garçons et 5 filles. Deux patients étaient âgés de plus de 10 ans au moment du diagnostic du PTI aigu. Les symptômes au stade chronique étaient des hémorragies cutanéo-muqueuses. Une patiente a présenté une hémorragie cérébrale post traumatique. Trois patients ont présenté une forme sévère et ont nécessité un traitement de deuxième ligne. Deux patients ont reçu Eltrombopag avec une bonne réponse. Un patient a eu une rémission spontanée après 3 ans de suivi.
Conclusion: La prise en charge du PTI chronique constitue un véritable défi pour les pédiatres. Actuellement, il existe certaines recommandations et directives qui peuvent guider la stratégie de prise en charge des formes sévères du PTI chronique.

Mots clés: purpura thrombopénique immunologique ; chronique ; enfants; prise en charge

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Introduction

Immune thrombocytopenic purpura (ITP) is one of the most common acquired bleeding disorders, occurring in ~5 to 10 per 100 000 children per year; 10 to 25 % of children develop chronic immune thrombocytopenia which is defined by the persistence of thrombocytopenia more than 12 months [1,2].

Even; the management of acute ITP is relatively consensual; there is no consensus for the management of chronic ITP. Therapeutic options in chronic ITP depends on the severity of bleeding symptoms; these includes therapeutic abstention for asymptomatic CITP, immusuppressive agents, thrombopoietin receptor agonists (TPO-RAs), and splenectomy. The oral TPO-RA eltrombopag was approved by the US Food and Drug Administration (FDA) for use in children with chronic ITP in 2015 [3].

Management of chronic ITP in children represents a real challenge for pediatrician; in fact , he must firstly exclude all other conditions which can result in thrombocytopenia such as bone marrow aplasia, dysimmune pathologies, thrombopathies, Willebrand type 2 B and hereditary immune deficiency , secondly , he must choose the adequate therapeutic strategy for management of severe forms of chronic ITP considering that the management of chronic ITP remains nonconsensual. Immune thrombocytopenia (ITP) is the most common autoimmune cytopenia in children. Very few studies were carried out in the Maghreb concerning ITP in children.

Here in, authors reported 11 children with chronic ITP; they describe clinical features, bleeding symptoms, management strategies and evolution.

Methods

We conducted a retrospective study for above than 12 years (from 1st January 2010 to 31 December 2022), we collected all cases of chronic ITP among children aged less than 14 years who were diagnosed and treated in the department of pediatrics, Hedi Chaker Hospital Sfax Tunisia.

Inclusion criteria: children between the age of one and 14 years, presenting chronic ITP which is defined as ITP that lasts longer than 12 months [4].

Exclusion criteria: children having secondary immune thrombopenia

The diagnosis of newly diagnose ITP is based on clinical features: isolated bleeding (sudden onset bruising, petechiae, mucosal bleeding symptoms such as epistaxis), no organomegaly or lymphadenopathy), and isolated thrombopenia in the complete blood count.

In addition to family history and meticulous examination, children with chronic ITP underwent some investigations in order to rule out differential diagnosis which included:

- Blood smear + mean platelet volume (MPT) (normal values: 7-12 femtoliters)
- Primary hemostasis evaluations to rule out associated thrombopathy (platelet aggregability test if platelet's count is above 50000/mm3 or flow cytometry of platelet proteins)
- Von Willebrand Factor antigen (VWF Ag): normal values (50-150%)
- VWF ristocetin cofactor assay (VWF:RCo): normal values (50-150%)
- Antinuclear antibodies (ANA): significantly elevated when ≥ 1/160
- direct coombs test
- Immunogical assessment: a weight immunoglobulins dosage, immunophenotyping of circulating lymphocytes, lymphocyte proliferation tests, double negative T cells (CD3+, CD4- , CD8-) and CD95 expression.
- Bone marrow aspiration (if it wasn't been done in the acute stage) ± medullary caryotype to exclude central etiologies of thrombopenia.
- Screening for Hepatitis B and C , HIV and Helicobacter pylori (PCR HP in the stool)
- All these investigations were repeated annualy.

The severity of the bleeding was assessed according to the easy and quick Buchanan-Adix score [5]. This ranks the hemorrhagic syndrome from 0 to 5, depending on the extent of the hemorrhage and the organs affected.

First line treatment modalities for acute bleeding was based on the severity of the bleeding; it consists on administration of a single dose of polyvalent immunoglobulins (0.8 to 1 g/kg) or a short course of oral corticosteroids (prednisone or prednisolone): 4mg/kg/day in one or two doses (max 120mg/day) for 4 days [6].

Severe forms of chronic ITP are defined by recurrent bleeding symptoms requiring treatment with the impairment of life quality and life -threatening bleeding.

In the event of life-threatening bleeding, we associated platelet transfusions, immunoglobulins and corticosteroid therapy.

A second-line therapy was indicated for these severe forms, which included [6]:

- Azathioprine: at the daily dose of 2 mg/kg
- Mycophenolate mofetil: 1200mg/kg per day (maximum of 2000mg)
- Rituximab: 375 mg/m2 per week for 2-4 weeks
- Oral thrombopoietin receptor agonist (TPO RA): Eltrombopag with initial dose of 50 mg per day

A complete response was defined as a platelet count>100×10^9/L and absence of bleeding.

A partial response was defined as a platelet count between 30×10^9/L and 100×10^9/L with at least a doubling of the baseline count and the absence of bleeding.

No response was defined as a platelet count < 30 $x10^9$, less than a doubling of the baseline count or bleeding events when the patient had received an appropriate dose of the second line drug for three months [4].

Results

During the study period, 11 children with chronic ITP were enrolled. During the same period, 72 cases of newly diagnosed ITP were collected, thus the proportion of chronic ITP was 12, 5 %.

They were 6 boys and 5 girls. The age at diagnosis of

acute ITP varied between 13 months and 12 years and 9 months (median: 7 years and 8 months). Five patients were aged more than 8 years. There is no significant family history.

For patients with newly diagnosed ITP, circumstances of the detection were fortuitous in two cases. Cutaneous bleeding (petechias, bruises) was noted in six cases (grade 1-2 of score of Buchanan) , epistaxis in two cases and menorrhagia in one case (grade 3 of score of Buchanan)

At the chronic stage of the disease, three patients presented severe forms; a boy had constantly low platelet count and recurrent epistaxis, another boy had isolated thrombocytopenia (less than 10000/mm3) and a girl with frequent gingivorrhagia, nose bleeding and menorrhagia.

At the onset of the disease, platelet count varied between 2000/mm3 and 87000/m3(median : 7000/mm3). Five patients had a platelet count below 10000/mm3.

Peripheral blood smear was performed in 9 children ; it showed enlarged platelets in three cases and no abnormal cells. Haemostasis screening tests were normal in all cases.

Bone marrow aspiration was perfomed for all patients and was consistent with peripheral thrombocytopenia.

During the chronic stage, in order to exclude others conditions which can lead to secondary ITP such us dysimmune pathologies (primary immunodeficieny, systemic lupus erythematosus , ALPS syndrome), infections, and constitutional thrombocytopenia , we considered medical history and clinical examination, moreover, some laboratory investigations were performed ; it includes antinuclear antibodies (ANA) , direct coombs test (DCT), platelet aggregation tests or flow cytometry, Von Willebrand factor antigen (VWF Ag) , ristocetin cofactor activity of VWF (Rco VWF Ag), screening for Hepatitis, HIV and *Helicobacter Pylori* and immunological assessement to rule out primary immunodeficiencies (Table 1). Patients with positive antinuclear antibodies , had no clinical manifestations of systemic lupus erythematous and other antibodies were negative (DNA antibodies, anti RNP, anti SSA, antiSSB).

Table 1. Investigations in order to exclude differential diagnosis

	ANA	DCT	MPV	Platelet aggregation or flow cytometry	VWF Ag (%)	VWF : Rco (%)	Screening for Hepatitis , HIVand HP	Immunological assessment
Patient 1	neg	neg	12,7	N	120	95,2	neg	N
Patient 2	1/80 and 1/320	neg	7,5	N	69	61	Neg HP :ND	N
Patient 3	1/80	neg	-	ND	120	80	HP :pos	N
Patient 4	neg	neg	9,6	ND	120	100	HP : pos	N
Patient 5	1/320	neg	9,2	N	82,5	82,5	neg	N
Patient 6	neg	neg	-	N	ND	ND	neg	N
Patient 7	1/320	neg	-	N	75	159	neg	N
Patient 8	neg	neg	8,8	N	116	116	HP : ND	N
Patient 9	1/320	neg	9,9	N	ND	ND	HP : pos	N
Patient 10	1/160	neg	12,2	ND	241	280	neg	N
Patient 11	1/160	neg	8,8	ND	N	N	HP : pos	N

ANA : antinuclear antibodies,**DCT** : direct coombs test, **MPV** : mean platelet volune, **neg** : negative, **N** : normal, **ND** : not done, **pos** : positive, **HIV** : Human immunodeficiency virus, **HP** : Helicobacter Pylori, **VWF Ag** : Von Willebrand factor antigen, **VWF Rco** : VWF ristocetin cofactor assay

During the chronic stage, seven patients required corticosteroid treatment (prednisolone at a dose of 4 mg/kg/day for 4 days) or intravenous immunoglobulin (1g/kg) by pulse on demand.

The three patients who presented a severe form , a second-line treatment was started. (Figure 1).

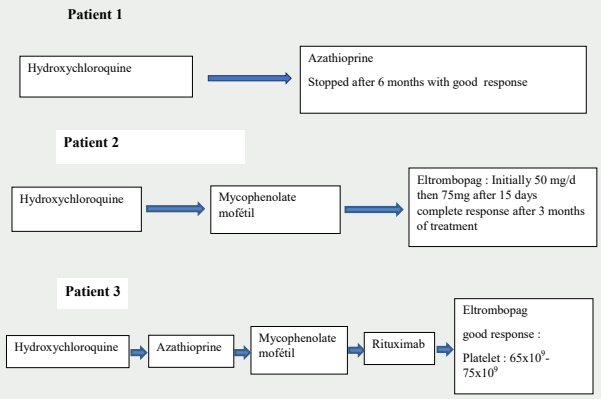

Figure 1. management strategy of patients with severe form of Chronic ITP

Each drug with no response after 3 months of treatment was stopped (platelet count < 30000/mm3). No side effects of the different drugs were noticed.

One patient developed post traumatic intra cerebral hemorrhagia ; the patient suffered from vomiting, headache and right hemiparesis , a brain CT scan showed a left parietal intraparenchymal hematoma (5 cm) with mass effect (figure 2) ; she had received association of methyprenisolone (30 mg/kg max 1g), intravenous immunoglobulin (1g/kg/day) and platelet transfusion for three days. Moreover, she received a unique dose of recombinant Factor VII (90 µg/kg). She had evolved favorably with no neurological saquelae. A brain scan was performed one month later showed a complete resolution of the hematoma.

We recorded one case of spontaneous remission after 3 years of follow-up. Seven children were followed in the outpatient department with a follow-up varying between 1,5 and 6 years; they presented a moderate ITP with no impact on health quality of life. The three other patients presented a severe form ; one of whom, who was described above, presented post traumatic intracerebral bleeding during the course.

Three patients were transferred to the department of hematology at the age of 15.(Table 2)

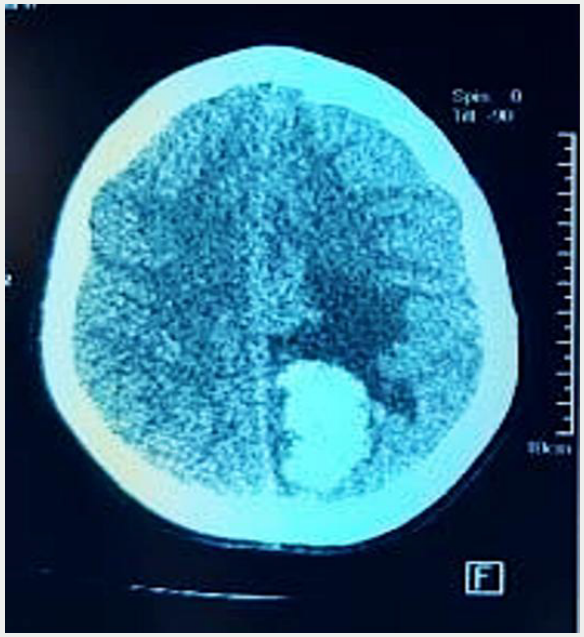

Figure 2. Brain CT scan : left parietal intraparenchymal hematoma (5 cm) with mass effect

Table 2. clinical course, complications and follow up of the patients

	Severity/ Complications	Follow up duration	Final outcome
P1	moderate	5 years	Last platelet count : 128000/mm3
P2	moderate	4 years	Last paltelet count : 97000/mm3
P3	Moderate	3 years	Spontaneous remission
P4	moderate	6 years	Transferred to the department of hematology at the age of 15
P5	moderate	2 years	Last platelet count : 88000/mm3
P6	moderate	3 years	Last platelet count : 67000/mm3
P7	severe	3 years	Last platelet count : 97000/mm3
P8	moderate	3 years	Last platelet count : 56000/mm3
P9	severe	1,5 years	Transferred to department of hematology at the age of 15
P10	moderate	2 years	Last platelet count : 44000/mm3
P11	Severe form , intracerebral hemorrahagia with favorable evolution	1,5 year	Transferred to department of hematology at the age of 15

Discussion

Epidemiological data on the incidence of chronic ITP in children are relatively limited and vary considerably depending on the data source, methodology and study period . It has been estimated at 1 in 250,000 children per year [7,8]. The percentage of progression towards chronicity of children with ITP varied according to the studies is 10 to 30 % [9-11].

The transition to chronicity is lower in infants, around 10% , however, it is higher (nearly 50%) in children older than 10 years [12].

The progression to chronicity is similar between girls and boys in young children . However, during adolescence, it is more common in girls [13].

Major predictive factors for developing chronic ITP in the literature were found to be age of more than 10 years old at presentation , female sex and the number of platelet at the onset of the disease (>10 x10^9/L.) [11, 14]. In our study, sex ratio was ~ 1 and two patients were aged more than 10 years at the onset of the disease.

Depending on the severity of thrombopenia, patients are at increased risk of bleeding. Although serious bleeding is more likely to occur with a platelet count < 20 × 10^9/L, most children with chronic ITP with this platelet count will not have significant bleeding [15,16]. The most common bleeding events during chronic ITP is cutaneous bleeding, such as petechiae and bruising, followed by epistaxis [16,17]. Intracranial hemorrhage is considered as a rare complication occurring in approximately 1% of cases in several studies [18,19]. In a study conducted in the United States, collecting 40 cases of intracranial hemorrhage in patients with ITP aged less than 17 years; 28 cases occurred at the onset of ITP and 12 cases in the chronic phase. The risk factors for the occurrence of intracranial hemorrhage were the presence of trauma or macroscopic hematuria. The number of platelets was less than 20,000/mm3 in 90% of cases and less than 10,000/mm3 in 75% of cases. The outcome was fatal in 10 patients and 10 other patients had neurological sequelae [19].

In our study,the most frequent bleeding symptoms in the chronic stage were mucosal bleeding (epistaxis, menorrhagia,) and only one patient presented post traumatic intracerebral hemorrahgia.

During chronic ITP, the assessment of the severity of bleeding signs is based on several severity scores ; one of the simplest scores is Buchanan score ; a clinical score which assessed the severity of bleeding independently of the platelet level [5].

Severity is defined by the presence of bleeding symptoms requiring initiation of treatment or an increase in dose or a change in treatment [4]. It is therefore clinical and not biological and is characterized by permanent or frequent hemorrhagic syndromes or clear impairment of Health quality of life [12].

In the case of chronic ITP in children, physician faces two challenges ; firstly, he must exclude secondary ITP and secondly he must choose the appropriate treatment for patients with severe forms. Primary ITP remains a diagnosis of exclusion. A careful history and clinical examination are mandatory to search a sign pointing to another diagnosis or an associated pathology. Moreover, some investigations are requested ; it includes a blood count with the reticulocyte level, the mean platelet volume, a blood smear, the dosage of VWF Ag and the ristocetin activity of the VWF, screening for infections (HIV and Hepatitis B , C and *Helicobacter Pylori*), antinuclear antibodies, direct coombs test to look for possible Evans syndrome, an ADAMTS 13 activity assay if there are clinical or biological signs of hemolysis with a negative coombs test, an immune assessment to look for primary immudeficiency and genetic study of constitutional thrombocytopenia [20]. Myelogram

associated with medullary caryotype must be performed if it wasn't been done at the onset of the disease

The management of chronic ITP remains complex and non-consensual. There are currently guidelines to facilitate this management [4,6,20]. The majority of cases do not require any treatment, particularly in the absence of mucosal hemorrhage or a Buchanan score less than or equal to 2 or a platelet count greater than 10,000-20000/mm3 without hemorrhagic symptoms

In the case of mucosal bleeding and before invasive gesture or surgery, short-term corticosteroid therapy or intravenous immunoglobulin may be proposed [20]

For patients with life-threatening bleeding, combined strategies must be implemented. This generally involves standard therapy (immunoglobulin and corticosteroids) often associated with platelet transfusions 5 and eventually the use of thrombopoietin receptor agonists (TPO-RAs).

For children with chronic ITP who have frequent non-life threatening mucosal bleeding and/or diminished health quality of life, second-line treatment is requested. Recurrent or prolonged courses of steroids should be avoided in children with ITP due to their known short- and long-term toxicity as well as the availability of other alternative therapies with fewer side effects [6]

Second line treatment's options include immunosuppressants (azathioprine, hydroxychloroquine, mycophenolate mofetil and rituximab) ,thrombopoietin receptor agonists and splenectomy.

Hydroxychloroquine is indicated especially in children aged over 6 years with significant levels of antinuclear antibodies (> 1/160) [20]

The duration of treatment with azathioprine and mycophenolate mofetil should not exceed 18 to 24 months, in the event of a good response .

Rituximab is a monoclonal antibody specifically targeting B lymphocytes by binding to the CD20 antigen. Pooled data from a systemic review of pediatric studies reported that the complete response rate to rituximab is 39%, with a median duration of response of only 12.8 months [21].

Thrombopoietin receptor agonists (TPO-RAs) represent a class of platelet growth factors used in the management of ITP in children and adults [22] ; In patients with chronic ITP who have mucosal bleeding and/or impaired quality of life and do not respond to first-line therapy, the ASH suggests the use of TPO-RA rather than rituximab [6].

Eltrombopag is a TPO-RA, which received Marketing Authorization in 2015 for use in children aged over one year and suffering from chronic ITP [3].This oral therapy, to be taken once a day, has demonstrated favorable effectiveness as well as good tolerance in children.

It increases the platelet count in a few weeks, thereby reducing the risk of major bleeding and improving quality of life .

In a multicenter randomized study called PETIT2 conducted in 38 centers in 12 countries reported by Grainger and al, 40% of patients receiving eltrombopag achieved an increase in platelet counts to more than 50,000 /mm3 between the fifth and twelfth week of treatment [23]. The starting dose of 50 mg per day for patients aged 6 years or older, and 25 mg per day for patients aged between 1 year and 6 years.

Once initiated, the eltrombopag dosage should be adjusted to achieve a platelet count goal of 50,000/m3. The pre-therapeutic and monitoring assessment includes an ophthalmological examination looking for cataracts and liver function tests (transaminases, bilirubin).

In our study, two patients have taken Eltrobompag with good response (platelet > 50000/mm3) after 4 and 6 weeks respectively.

It should be noted that some treatments, although potentially effective, may require an extended period of 3 to 4 months to evaluate their impact, using pharmacological dosages when available and validated to optimize the balance between benefits and risks .

Splenectomy represents a curative treatment in 70 to 90% of cases after the age of 5 years [12]. It should be reserved for children aged over 10 years after failure of two second-line treatments [20]

The course of chronic ITP is unpredictable. Remission is defined as a platelet count > 100,000/mm3 on two occasions in the absence of continuous or long-acting platelet therapy [6,16]. Several authors have reported that the possibility of remission persists for many years after diagnosis (24-26). The percentage of this remission varies between 24% and 63% depending on the studies (27,28). In our study, spontanoues recovery was observed in a child after 3 years of follow up.

Complications during chronic ITP are of two types ; those linked to the disease, mainly cerebro-meningeal hemorrhage, and those linked to side effects of treatments. Cerebro-meningeal hemorrhage is a significant cause of morbidity and mortality but is fortunately rare.

Conclusion

The diagnosis of chronic ITP should only be made after excluding other diagnoses through an exhaustive diagnostic work-up. Severe chronic ITP that impairs the child's quality of life requires second-line treatment. Thrombopoietin receptor antagonists represent a promising therapeutic pathway for severe chronic ITP.

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