Primary and secondary Immune thrombocytopenia in Moroccan children

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Abstract

Immunological Thrombocytopenic Purpura or ITP is the most common benign blood disease in pediatrics. The aim of this work is to analyze the epidemiological, clinical, paraclinical and etiological profile of Primary and secondary immune thrombocytopenia. It is a retrospective study over a period of four years from September 2017 to September 2021, collecting all cases of immunological thrombocytopenic purpura hospitalized in hematology pediatric unit at the Abderrahim Harouchi Children's Hospital in Casablanca. 135 patients with ITP were hospitalized in this period including 76 boys (56.3%) and 59 girls (43.7%). The average age was 5.8 years (1 month -14 years). According to Buchanan bleeding score, 3.4% of the patients were grade 0, 9.6%, were grade 1 and 39.2% of the patients were grade 2, 41.5 % of the patients were grade 3, 5% in grade 4 and only 1 case was in grade 5. Etiologically, 86% of primary ITP and 14% of secondary ITP were recorded. The etiological assessment revealed 9 cases of Helicobacter pilori infection, 6 cases of immune deficiency (5 cases of WISKOTT ALDRICH and 1 case of ALPS) and4 probable cases of systemic lupus erythematosus. Patients were treated with either corticosteroids or intravenous immunoglobulin (IgIV). The trend was towards acute ITP in 85 cases (63%), persistent and chronic ITP in 50 cases (37%). For a better management of chronic and persistent ITP a complete etiological assessment is essential. This will allow to propose an etiological treatment and therefore an improvement of thrombocytopenia.

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Abbreviations

ITP	Immune thrombocytopenic purpura
SLE	Systemic lupus erythematous
IVIG	Intravenous immunoglobulin
HIV	human immunodeficiency virus
PCR	Polymerase chain reaction
SARS-COV-2	severe acute respiratory syndrome coronavirus 2.

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INTRODUCTION

Immune thrombocytopenic purpura (ITP) is the most common benign hemopathy in pediatrics, it is defined as an acquired autoimmune bleeding disorder with a low platelet count, usually, less than 100,000 in the presence of a generalized petechial rash, bruising, or bleeding in an otherwise healthy child [1].The incidence of ITP ranges from 1.1 to 6.4 cases per 100,000 children-years with peak in childhood (age 1–5 years) [2,3]. There is a slight predominance in males than females [4].

The classification of ITP depends on the duration of disease based on the following definitions: newly diagnosed (from diagnosis to three months), persistent (3-12 months), and chronic (after 12 months) [3,5].

Chronic ITP is seen in 10 to 25% of these patients with a prevalence estimated as 9.5 to 11.2 per 100,000 persons year [3].

The ITP etiology should be sought in the presence of a recurrent or chronic ITP. Most cases are considered idiopathic and labelled as 'primary ITP', whereas approximately 20% of ITP cases are associated with an underlying disorder and are labelled as 'secondary ITP'[3]. This secondary ITP can be due to infection with a number of agents, including hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Helicobacter pylori. Other causes include underlying autoimmune and lymphoproliferative disorders such as systemic lupus erythematosus, Wiskott-Aldrich syndrome, and common variable immunodeficiency, as well as drugs such as trimethoprim-sulfamethoxazole [3].

The ITP patients are usually treated with steroids or immunoglobulin as a first line treatment. For chronic ITP the traditional therapies are rituximab and splenectomy [3]. Mortality from ITP in children is rare and mainly due to complications from catastrophic bleeding, specifically intracranial hemorrhage [1]. The disease is self-limiting in a large proportion of patients, and 75% to 90% of children will recover spontaneously within 6 to 12 months [2,6].

The aim of this retrospective study is to highlight the frequency of secondary ITP among ITP patients, to precise the specificities of theses patients, and to determine the etiological profile of the ITP in children.

MATERIALS AND MEHODS

In this retrospective study, 135 ITP patients admitted in Hematology-oncology unit in pediatrics 3 Department, A. HAROUCHI University Hospital, Casablanca, Morocco, between September 2017 and September 2021 were included. Patients were included in this study if their age at diagnosis was less than15 years, and their platelet count was low (less than 100 000/mm3). Exclusion criteria included the following: the presence of mild splenomegaly and having received treatment that may cause drug-induced thrombocytopenia. The demographic and clinical characteristics of patients at the initial diagnosis of ITP were abstracted from their medical records. These data included age, gender, initial platelet count, initial presentation of mucocutaneous purpura.The bleeding was assessed using the BUCHANAN score (grade 0, grade 1, grade 2, grade 3, grade 4 and grade 5). Patients were graded based on their medical history or a physical examination completed at the time of the appointment. Grade 1 is few bruises and petechiae. Grade 5 is life threatening hemorrhage. Furthermore, data about the need for treatment of ITP and the response to treatment were collected. The screening for antinuclear antibody (ANA), hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), immunoglobulin dosage and lymphocyte phenotype were tested in the patients with chronic ITP. The H. pylori stool antigen test or the urea breath test were used to screen patients for H. pylori were abstracted from the medical records.

RESULTS

A total of 135 children who were diagnosed with ITP at our unit between September 2017 and September 2021 and were included in this study. Their age at diagnosis ranged between 1 month and 14 years, with a mean of 5,8. There were 76 boys (56.3%) and 59 girls (43.7%). According to Buchanan bleeding score, 3.4% of the patients (5 cases) were grade 0, 9.6% (13 cases), were grade 1 and 39.2% of the patients (53 cases) were grade 2, 41.5 % of the patients (56 cases) were grade 3, 5% in grade 4 and only 1 case was in grade 5.

116 patients (86%) were diagnosed as having primary ITP and 19 (14%) were considered to have secondary ITP because the ITP was associated with another underlying disorder or condition. Among the 135 children, 85 patients (62.9%) had an acute ITP and 50 patients (37%) had a chronic ITP. In these chronic ITP, a concurrent immune disease was observed in 19 (38%) patients who were diagnosed with secondary ITP. Of those who were diagnosed with secondary ITP, 6 (31,5%) had primary immune deficiency and 4 (21%) had systemic lupus erythematosus. The 9 remaining patients (47.3%) had a helicobacter infection. All patients were tested for the presence of HCV, HBV, and HIV, and none tested positive. In patients with primary immune deficiency we found 5 cases of Wiskott Aldrich syndrome. All these patients had thrombocytopenia, eczema and recurrent infections.

Table 1 shows the characteristics of patients with primary and secondary ITP. Patients with secondary ITP were slightly younger than patients with primary ITP. The mean age was 6 years for patients with primary ITP and 5.4 years for patients with secondary ITP. Among patients with secondary ITP, the mean age of patients with a primary immune deficiency (mean: 3.7 years) was lower than that for patients with other disorders (mean: 6.5 years). At the time of diagnosis, 74% of patients with secondary ITP and 62% patients with primary ITP had an initial platelet count >30 109 /L. Among patients with secondary ITP, the median initial platelet count for patients with a primary immune deficiency was slightly higher (34 109 /L) than that for patients with other disorders (23 109 /L). At the time of diagnosis, the Buchanan bleeding score was higher than 2 in 48 % of patients with primary ITP and in 37% of patient with secondary ITP. The two groups had poor response to corticosteroid treatment (less than 20% had good response). However, the primary ITP patients had good response to immunoglobulin in 55% of cases versus 14,8% of good response in the secondary ITP patients.

Table 1. Clinical, laboratory characteristics and response of treatment of the whole cohort of 143 patients

Feature	Primary
Number (Percentage)	116 (86%)
Sex: Boys Girls	66 (56.8%) 50 (43.1%)
Age, mean Age < 3 years 3 years < Age < 6 years 6 years < Age < 12 years Age > 12	6 24 (20.6%) 42 (36.2%) 32 (27.5%
Bleeding score Grade 0 Grade 1 Grade 2 Grade 3 Grade 4 Grade 5	4 (3.4%) 12 (10.3%) 41 (35.3%) 5(
Platelet count at diagnosis 0 -10 109 /L 10- 30 109 /L >30 109 /L	44 (37.9%) 51 (43.9%) 21 (18.1 %
Response to immunoglobulin Yes No	64 (55.1%) 52 (44.8%)
Response to steroids Yes No	22 (18.9%) 94 (81.1%)

DISSCUSSION

There is a paucity of references regarding the differences between characteristics of primary and secondary ITP in the pediatric population. This study demonstrates the importance of a correct diagnosis of secondary ITP and highlight different causes of this type of ITP.

Primary immune thrombocytopenic purpura (ITP) remains a diagnosis of exclusion for immune thrombocytopenia. Most cases are considered idiopathic, whereas secondary ITP should be ruled out to predict the outcome and to choose the right treatment [4]. Newly diagnosed ITP is a relatively common disorder of childhood that does not require an exhaustive laboratory workup for diagnosis. 15–20% of cases of ITP in children develop chronic ITP and lead to impaired quality of life, whereas life-threatening bleeding, such as intracranial hemorrhage, is uncommon in these children [7]. In our study, 37% of ITP patients had a chronic ITP and only one presented an intracranial bleeding with good outcome after treatment.

In 75% to 90% of patients, the disease has a transient, self-limiting character. The polymorphisms of FcgR genes may affect disease susceptibility, response to intravenous immunoglobulin treatment, and long-term recovery from childhood ITP [6]. Risk factors associated with an increased risk of developing chronic ITP include older age at diagnosis, less severe thrombocytopenia at initial diagnosis, gradual onset of symptoms, absence of preceding infection or vaccination prior to ITP diagnosis, and absence of mucosal bleeding at presentation [1].

According to previous reports, 80% of ITP are considered idiopathic and 20% are secondary to coexisting conditions [4]. In a recent French population-based study, Moulis and al found that ITP was secondary in only 2.4% of children, in whom primary immune deficiency (PID) and Systemic lupus erythematous (SLE) were the most common cause [3]. In our study we found 86% of primary ITP and 14 % of secondary ITP.

The first important point in our series, is to distinguish the difference between primary and secondary ITP characteristics. We found that the onset of secondary ITP to primary immunodeficiencies (PID) was at a younger age and had more tendency to be insidious, and platelet level was slightly higher than primary

ITP. Whereas treatment response was significantly higher in primary ITP and it was worse in PID and SLE patients. Therefore, the presence of these characteristics should alert physicians to recommend periodical studies in order to exclude these disorders.

The second important point of this study is that ITP might also be the first manifestation of an underlying disorder. In our series, 19 patients were diagnosed with an PID, an SLE or HP infection after the initial ITP diagnosis. These patients showed no tendency to remit spontaneously nor under first line treatment. Therefore, the Identification of secondary ITP is important as it predicts outcome. And they should be ruled out periodically as they are usually identified later. Elsewhere, the diagnosis of secondary ITP should be suspected in the presence of medical history of recurrent infections, failure to thrive, eczema and microplatlets and treatment unresponsiveness.

This result is comparable with other reports who find that isolated ITP can be an initial sign of autoimmune disorders in children. Systemic lupus erythematous (SLE), Evans syndrome, autoimmune lymphoproliferative syndrome (ALPS), HIV, viral hepatitis and primary immunodeficiencies may initially present as thrombocytopenia. Further evaluation is warranted in patients who have had recurrent or chronic ITP especially if they have had poor response to IVIG and steroids [2,8,9]. Furthermore, immunoglobulins as a part of a reassessment evaluation should be periodically tested in those children [2].

The risk of developing primary immunodeficiencies (PID) following the onset of ITP has been extensively examined [2]. PID may be present in 2 to 11 percent of ITP patients. PID ITP patients are more likely to fail first line therapy. Therefore treatment- refractoriness may offer some additional guidance regarding which patients require additional screening for PID [4,10,11,12]. In our study, a primary immunodeficiency (such as WISKOTT ALDRICH or ALPS) is found in 4.5% of cases with thrombocytopenic purpura which is equivalent to the finding in the literature.

In common variable immunodeficiency, ITP occurred in 7.6% of the patients and it should be suspected in patients with recurrent ITP, Elsewhere ALPS can be found in 1% of IPT. [10,13]. Wiskott-Aldrich syndrome (WAS) is a rare X-linked primary immunodeficiency disease (PID) characterized by thrombocytopenia, eczema, recurrent infections, and an increased incidence of autoimmunity and malignancies [15]. Its incidence is estimated to 1 to 10 per million children in the United States and Europe [16]. WAS in children are often first diagnosed with ITP, potentially leading to both inappropriate treatment and a delay in definitive life-saving therapy. WAS is detected in 7% of ITP patients [15,16,17]. It has traditionally been distinguished from ITP by the small size of the PLTs seen in WAS patients. As a result, the WAS gene diagnosis should be considered in all males with ITP-like symptoms, particularly those with a very early onset age, decreased MPV (6.5 fl), higher EOS counts, and elevated IgE level, increased NK cell number and diminished CD8+T lymphocyte count [15,16]. In our study we found 5 cases of WAS (3.7%) revealed by ITP of which 3 are confirmed genetically. All of these patients were males with the clinical triad: thrombocytopenic purpura, eczema and recurrent infections.

The systemic lupus erythematosus (SLE) is a connective tissue disorder with variable presentations in children. The usual presentation includes arthritis, malar rash, nephritis, hemolytic anemia, and fever. Isolated hematological manifestation of SLE in children is a rare entity, and it occurs in the form of hemolytic anemia, thrombocytopenia, and persistent leukopenia [18]. In general, it's a female child with isolated bleeding and low platelet count. When platelet count didn't go up despite appropriate treatment in lines of ITP, further investigations are done to make diagnosis of SLE [18]. Positive ANA are reported in 10% of ITP patients and 4% of them developed criteria consistent with SLE [2]. In our study, 4 patients (2.9%) with ITP presented positive AAN and were transferred to the rheumatological unit to further assessment and specific treatment.

Other causes of secondary ITP can be seen such as infections like HIV, hepatitis c, and HP infection. Approximately two-thirds of children with ITP have a history of an infection during the prior month. Viruses commonly identified as triggers include cytomegalovirus, hepatitis C, herpes, varicella zoster, Epstein-Barr, influenza, and HIV [19]. Among HIV positive patients, thrombocytopenia is a common feature. Various studies indicated that about 5% to 10% of HIV infected patients develop thrombocytopenia during the

course of the disease, and ITP may be the sole clinical manifestation of HIV infection. Steroids, IVIGs, and antiretroviral therapy have all been tried with fall in platelet count on withdrawal of therapy [5]. Hepatitis C virus has been reported to be associated with the occurrence of autoimmune disorders, including ITP. A study with 150 subjects reported that the prevalence of severe thrombocytopenia was significantly higher in ITP patients compared with that in chronic HCV patients [5]. During the SARS-CoV-2 pandemic, it is important to remember the association between isolated thrombocytopenia and COVID-19 and to include the PCR for SARS-CoV-2 in the laboratorial investigation and follow-up, as ITP can develop [20].

Immune thrombocytopenia has been shown to be linked to *H. pylori*infection. The prevalence of H. pylori infection is 70% in Japanese ITP patients, 22% in North American chronic ITP patients, 29% in patients with ITP of white French origin [5]. In our study we found this HP infection in 6.6% of ITP patients. The pathogenic link between *H. pylori* infection and PIT might be the molecular mimicry between platelet surface glycoproteins and amino acid sequences of *H. pylori* [21]. Based on recent systematic reviews, more than half of patients have successfully recovered platelet counts following *H. pylori* eradication treatment [22,23]. However, response rates vary widely across geographic regions, with highest response rates reported in Japan and Italy [5,24]. Therefore, they suggest that the group of ITP patients from highly endemic regions should be considered for H. pylori detection testing and therapy [5].

The ITP patients are usually treated with steroids or immunoglobulin as a first line treatment. For chronic ITP the traditional therapies is rituximab and splenectomy. Thrombopoietin receptor agonists are newer agents for the treatment of chronic ITP and hold promise, however, their cost currently precludes use in most of the patients in low-middle-income countries [7]. Mortality from ITP in children is rare and mainly due to complications from catastrophic bleeding, specifically intracranial hemorrhage. The majority of mortality and morbidity in pediatric chronic ITP comes from complications of long-term immunosuppressive treatment, mainly infections [1,7].

CONCLUSION

The IPT can reveal an underlaying disease or condition such as a primary immunodeficiencies, a systemic lupus or un HP infection. The diagnosis of secondary ITP should be suspected in the presence of medical history of recurrent infections, failure to thrive, eczema and microplatlets and treatment unresponsiveness.

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