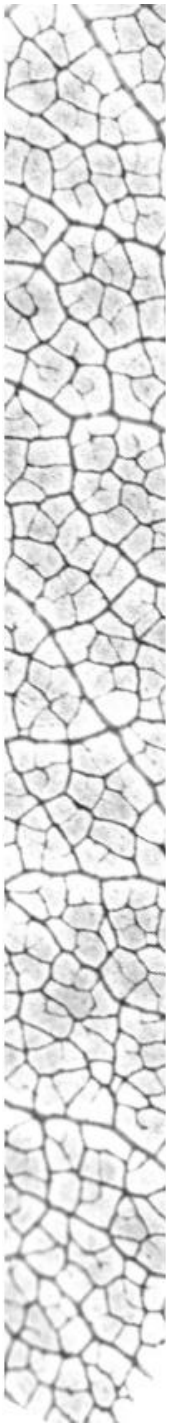

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Study of Immune Thrombocytopenia (ITP) in Iraqi's children in Wasit Province

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Abstract

Background: Immune thrombocytopenia (ITP) is an acquired hematological autoimmune disorder characterized by accelerates destruction of platelets with premature removal from circulation and inhibition platelets production. ITP is the most common cause of thrombocytopenia in childhood age group. Typically patients are otherwise well and present with petechiae, purpura and nonpalpable ecchymoses 1-3 weeks after a viral infection. The diagnosis of ITP remains almost one of exclusion and evaluation of history and examination of the patient. The goal of therapy in ITP is to increase the platelet count enough to prevent serious hemorrhage.

Aim of the study: To evaluate the possibility of diagnosis, follow up, effects of various treatment modalities on the clinical course and long term outcome in children with chronic ITP.

Materials and methods: The study was involved 78 patients (40 female and 38 male) were in age range 2-10 years referred to the Hemato-Oncology unit / Al-karama teaching hospital / Wasit / Iraq. Treatment options given to children with ITP during the study period including IVIG, Prednisolon induction, PRD maintenance, DAPSONE, Anti D, Decadron high dose, N platelet and Splenectomy.

Results: Male to female ratio was 1:1.05. Most of the patients (61.5%) were in age range 2-10 years, the mean of age was 72 months, range (2 months- 19 years). more than half of the patients were from center of Wasit province and seven patients were from another province. More than 80% of the patients (63) had no family history of Immune thrombocytopenia, while six patients were missed to record family history status. Fifty-five patients were sibling of consanguine father and mother. the highest number of patients was recorded in 2017 followed by 2012 and 2018. Majority of the patients presented with ecchymosis (seventy-one patients, 91%) while other types of presentation as conjunctival hemorrhage or epistaxis were recorded in less than 2.6% of the patients. Laboratory data of the patients with ITP shows that the mean Hb was 11.6 g/dl (8-15 g/dl) and mean WBC 4734 cmm (1400-25200 cmm), the platelet mean was 23000 cmm (1000-130 000 cmm). Forty-four patients did not have blood group. Bone marrow aspiration examination were done to forty five patients, the results of all them were normal. Specific investigations were done to patients with chronic ITP and according to what available in the hospital. Thirty-six patients (46.2%) were acute type and persist was reported in eight patients (10.3%) and chronic type was reported in thirty four (43.6%) patients. Most of the patients with acute ITP were with platelet count less than 20 000 cmm. While the highest percent of the patients with platelet more than 50 000 cmm were reported in chronic ITP. six patients didn't need treatment, and majority of the patients (92.3%) were treated with different types of treatment. From seventy two patients who received first line treatment, 67 patients (93.1%) were treated with prednisone induction plan. And five patients were treated with IVIG therapy when this drug was available in hospital, second line treatment was reported in 22 patients, prednisone daily low dose and dapsone was treatment plan in seven patients while five patients were received anti D as second line treatment. N plate medicine was reported in two patients and splenectomy was done for one patient.

Conclusion: at this study we found female patient with ITP more than male. The consanguinity was positive and most of patients used PRD induction as first line treatment, PRD maintenance and DAPSON mostly used as second line treatment and just three patients referred to third line treatment.

Keywords: biochemical changes, hormones, immune systems

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INTRODUCTION

Platelets are one of the three types of blood cells, along with red and white blood cells. It is colorless small sticky components in the blood which plays an important role in the first phase of hemostasis known as formation of platelet plug to prevent bleeding (Laki k, 1972), Normal platelets count are between 150-400 x 10A9/l, average life span between 7-10 days and then tapered into the spleen, normal platelet size between 1-4 ^m (younger platelets are larger), mean platelet volume

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(MPV) 8.9 +/- 1.5 ^m3, one third of its distribution in spleen and two third in circulation (Lanzkowsky 2011).

Immune thrombocytopenia (ITP) is an acquired hematological autoimmune disorder characterized by formation of antiplatelet antibodies that lead to accelerate destruction of platelets with premature its removal from circulation by macrophages of the reticuloendothelial system, also inhibit platelets production which influenced by drugs, infections, malignancy, or other autoimmune diseases. (Geddis, 2007; Bennett, 2009; Umit et al., 2019). ITP is classified into:Acute: usually occur in 80% of patients preceded by infection usually viral, self-limited and not lasting more than 6 months (Bennett, 2009), Persist: in this type thrombocytopenia lasts between 6-12 months. (Imbach et al, 2006), Chronic: mainly in old female, thrombocytopenia lasts more than 1 year (Lanzkowsky, 2011).

Diagnosis

The diagnosis of ITP remains almost one of exclusion and evaluation of history and examination of the patient.There are three diagnostic criteria:

1- CBC shows isolated thrombocytopenia (Provan et al. 2010).

2- Absence of hepatosplenomegaly, lymphadenopathy (Lanzkowsky,2011).

3- Platelet response to ITP therapy is the only finding that helps to positively support the diagnosis of ITP. (Lanzkowsky,2011; Neunert et al. 2011).

Additional laboratory analyses may be required:

1- Autoimmune screening—ANA and anti-double-stranded DNA antibodies, RA, C3, C4, etc. (George et al. 1996).

2- Thyroid screening (Lanzkowsky 2011).

3- Immune globulin measurements (IgG, IgA, and IgM) (George et al. 1996).

4- Liver function tests and H. pylori testing (Lanzkowsky 2011).

5- virology screen like EBV, CMV by PCR. (George et al. 1996).

Treatment

Treatment decisions should be based on the potential for bleeding including the physical activity level, patients history of bleeding, current platelet count, signs and symptoms and other factors (Neunert et al. 2011).

Corticosteroids

Corticosteroids create its impact by diminishing the generation of anti-platelet antibodies. Steroids moreover increase vascular solidness in ITP. Prednisone 1-2 mg/kg/day in divided doses orally for 2-4 weeks with tapering later on (George et al. 1996; Provan et al. 2010; Neunert et al. 2011).

Immune Globulin (IVIG)

IVIG appeared to be exceptionally compelling in raising platelet in more than 80% of patients. (Imbach et al. 1981; Ali, 2008). It acts by increase opsonized platelets survival, suppressing antibody production by B-cells. (Salama,1983).

Immune Globulin (IVIG) dose of 0.4-1 g/kg/day for 1-5 days. IVIG is preferred over steroids in children less than 2 years of age because they tend to have lower response rate to steroids and more challenging behavioral risk factors for bleeding (George et al, 1996; Provan et al. 2010;Neunert et al. 2011).

Anti-D therapy

It increases the survival of the opsonized platelets. It causes a rapid rise in platelet count comparable to IVIG response (Bussel et al.1991; Lanzkowsky,2011).

Splenectomy

Splenectomy is used for life-threatening bleeding which is not-respond to other medical treatment.. (Neunert et al. 2011)

Aim of the study

To assess the plausibility of determination, take after up, impacts of different treatment modalities on the clinical course and long term result in children with ITP in Wasit, Iraq

MATERIALS AND METHODS

This study was included 78 patients (40 female and 38 male) were in age range 2-10 years referred to the Hematology unit/Al-karama teaching hospital /Wasit/ Iraq. It involved patient with ITP, defined as having platelets count of <100 x 10A9 /L without identifiable cause (Neunert et al. 2011).

Treatment options given to children with ITP during the study period include

First line treatment : IVIG, Prednisolon induction.

Second line treatment: PRD maintenance, DAPSONE and Anti D

PRD maintenance Decadron high dose PRD maintenance, ANTID, IVIG Anti D DAPSONE, dexamethasone, Anti D with Dapson

Third line treatment: N platelet, Splenectomy (Yaprak et al, 2010)

Statistical analysis

Patient data were tabulated and processed using SPSS (Statistical package for the social sciences) V.20 for mac. P-value equal or less than 0.05 was considered significant.

RESULTS AND DISCUSSION

The demographic data of the patients who were treated in hemato-ocology center in Wasit province. Male to female ratio was 1:1.05. Most of the patients (61.5%) were in age range 2-10 years, the mean of age was 72 months, range (2 months- 19 years). more than half of the patients were from center of Wasit province and seven patients were from another province (Theqar and Mesan). More than 80% of the patients (63) had no

Table 1. Demographic data of the patients with immune thrombocytopenia purpura

Item	No	percent
Gender		
F	40	51.3
M	38	48.7
Age	group in years	
<=2	17	21.8
>210	48	61.5
>10	13	16.7
Address	Wasit center	41
	Wasit peripheral	30
	Theqar	6
	Mesan	1
	Family history of ITP	
	negative	63
	Positive	9
	Not recorded	6
	Consanguinity	
	Positive	55
	Negative	21
	Not recorded	2

Table 2. Frequency of cases of ITP according to year

Year of diagnosis	Frequency	Percent%
2008	1	1.3
2009	1	1.3
2010	12	15.4
2011	7	9.0
2012	6	7.7
2013	10	12.8
2014	2	2.6
2015	5	6.4
2016	**5**	**6.4**
2017	**17**	**21.8**
2018	**12**	**15.4**
Total	**78**	**100.0**

Table 3. Type of bleeding of the patients with immune thrombocytopenia purpura

Diagnosis	Frequency	Percent
Acute	36	46.2
Persistent	8	10.3
Chronic	34	43.6
Total	78	100.0

family history of Immune thrombocytopenia, while six patients were missed to record family history status. Fifty-five patients were sibling of consanguine father and mother, these demographic data were showed in **Table 1**.

Table 2 shows the number of the patients according to years, the highest number was in 2017 followed by 2012 and 2018, this pattern of distribution don't reflect the real number of the patients due to nature of health system in Iraq, as there is no clear establish referral system.

Majority of the patients presented with ecchymosis (seventy-one patients, 91%) while other types of presentation as conjunctival hemorrhage or epistaxis were recorded in less than 2.6% of the patients, **Table 3**.

Table 4 shows laboratory data of the patients with ITP, as the mean Hb was 11.6 g/dl (8-15 g/dl) and mean WBC 4734 cmm (1400-25200 cmm), the platelet mean was 23000 cmm (1000-130 000 cmm). Forty-four patients did not have blood group (which reflect poor

Table 4. Laboratory data of the patients with immune thrombocytopenia purpura

Blood group group	No	mean
Not done	44	56.4
A+	10	12.8
AB+	2	2.6
B-	1	1.3
B+	12	15.4
O+	9	11.5
B. M examination		
Not done	33	42.3
Normal cellular	45	57.7
VIH		
Not done	64	82.0
yes(-ve)	14	18
ANA & Ds DNA		
Not done	72	92.3
yes(-ve)	6	7.7

Item	No.	Mean	SD	Minimum	Maximum
Hb g/L	78	11.6	1.6	8	15
Wbc cmm	78	4734	4.7	1400	25 200
Platelet cmm	78	2300	25.9	1000	130000

Table 5. Diagnosis of the patients with immune thrombocytopenia purpura

Item	Frequency	Percent
Ecchymosis	71	91.0
Conjunctival hemorrhage	2	2.6
Ecchymosis & epistaxis	2	2.6
Gum bleeding	2	2.6
Epistaxis	1	1.3
Total	78	100.0

registration system in hospital). Bone marrow aspiration examination were done to forty five patients according to hematologist decision, the results of all them were normal. Specific investigations were done to patients with chronic ITP and according to what available in the hospital, are shown in **Table 4**.

According to scientific definition, the type of ITP was classified to acute, persist and chronic. Thirty-six patients (46.2%) were acute type and persist was reported in eight patients (10.3%) and chronic type was reported in thirty four (43.6%) patients, as shown in **Table 5**.

The correlation between ITP types and another variable as group of the patients and platelet count are shown in table number six. For platelet count variable, most of the patients with acute ITP were with platelet count less than 20 000 cmm. While the highest percent of the patients with platelet more than 50 000 cmm were reported in chronic ITP, although the correlation was statistically insignificant, p value more than 0.05. regarding age group, the lowest percent of the patients with age more than 10 years was reported in acute ITP, and highest percent of age group between 2-10 years was reported in same type (11.1%-66.7%) respectively.

As Iraq one of developing countries, not all treatment line available to the hematologist. **Table 7** shows treatment plan of the patients with ITP, as six patients didn't need treatment, and majority of the patients (92.3%) were treated with different types of treatment. From seventy two patients who received first line treatment, 67 patients (93.1%) were treated with

Table 6. Correlation of ITP types with platelet count and age group

Platelet count /cmm	Acute (%)	Chronic (%)	Persistent (%)	Total (%)	P value
<= 20 000	26 (72.2)	20 (58.8)	5 (62.5)	51(65.4)	0.7
21-49	5 (13.9)	7 (20.6)	2 (25.0)	14 (17.9)	
=>50	5 (13.9)	7 (20.6)	1 (12.5)	13 (16.7)	
Age group in years					
<=2	8 (22.2)	7 (20.6)	2 (25)	17 (21.8)	0.7
>2-10	24 (66.7)	20 (58.8)	4 (50)	48 (61.5)	
>10	4 (11.1)	7 (20.6)	2 (25)	13 (16.7)	

Table 7. Treatment data of the patients with ITP

Item	No.	Percent
Treated	72	92.3
Not treated	6	7.7
First line treatment of 72 patients		
IVIG	5	6.9
PRD induction	67	93.1
Second line treatment of 22 patients		
PRD maintenance, DAPSON	7	31.8
Anti D	5	22.7
PRD maintenance	4	18.2
Decadron high dose	2	9.1
PRD maintenance, Anti D IVIG	2	9.1
Anti D, DAPSON	1	4.5
PRD maintenance, Decadron high dose	1	4.5
Third line treatment		
N platelet	2	75
Splenctomy	1	25

prednisone induction plan. And five patients were treated with IVIG therapy when this drug was available in hospital. second line treatment was reported in 22 patients, prednisone dialy low dose and dapson was treatment plan in seven patients while five patients were received anti D as second line treatment. N plate medicine was reported in two patients and splenectomy was done for one patient.

DISCUSSION

The mean of age at time of diagnosis was 72 months, most of patients (61.5 %) were in age range 2-10 years. A study done in China by Zhao H. showed the same peak age. (Zhao et al. 2005)

As in this study we found more than half of patients were from center of wasit province and 9% were from another province, this variation may due to more population are live in center, or poor referral system and poor registration system.

As we attended many thrombocytopenic patients, we found more than 80% of the patients had no family history of Immune thrombocytopenia, while 11.5 % patients with positive family history and 7.7 % patients were missed to record family history status. In 2011, the PARC Registry on ITP (Kuhne et al. 2011) estimated that 2% of children and 3% of adults with ITP had family history with thrombocytopenia and some of these thrombocytopenias could be immune-mediated. As the first article on ITP cited in Pub Med was from January 1916. (Lee, 1916) although an undetermined number of articles had been previously published, according to these data we can estimate the annual incidence of familial ITP around 0.74 cases/year. It is a very low incidence when compared to the general incidence of ITP, estimated between 1.9 and 6.4 x 105 cases/year (Terrell et al. 2010).

In this research we observed that consanguinity had a relationship with ITP, as 70.5% of the result was positive, 26.9% was negative and 2.6% not recorded. There is no clear relationship between consanguinity and ITP but consanguinity is widely distributed in Asia and Africa especially in societies where Islam dominates and Arab countries which have an important contribution to many genetic defect and autosomal diseases (Al-Gazali et al.1995; Ali,2008).

Ecchymosis was the most recurrent sign that had found in patient with ITP as 91% but the absence of ecchymosis doesn't exclude the disease, while other signs were less than 9% such as conjunctival haemorrhage, Epistaxis and gum bleeding (Imbach et al. 2006).

Blood group not done for 56.4% of patients which reflect poor registration system in hospital. Bone marrow aspiration examination were done to 45 patients according to hematologist decision, the results of all them were normal which is necessary to exclude malignancy or bone marrow aplasia (Hijazi, 1994; Al-Mulla, 2009) However in other studies we found that bone marrow examination was unnecessary for the initial evaluation of newly diagnosed ITP patients (Elalfy et al. 2010) but if there is resistance or poor response to first line treatment then bone marrow is indicated (Grainger et al. 2010).

In this study we found 46.2% of patients had acute ITP, 10.3% had persistent type and 43.6 of patients had chronic type. These percentages cannot depend on precisely because of delay in diagnosis and neglect of parents in the follow up and treatment. However various studies reported that thrombocytopenia resolved in about 70% of children with ITP by 6 months (Watts, 2004; Bennett,2009) Also complete remission may achieved in a time longer than this period (Donato et al. 2009). The opportunities of spontaneous remission are still significant during long-term follow-up, both in adults and children (Stasi et al. 1995; Sailer et al. 2006)

In the result we connect the relationship between ITP types and other variable such as platelet count. The study shows that most patients with acute ITP were with platelet count less than 20000 cmm. While the highest percent of the patients with platelet more than 50 000 cmm were reported in chronic ITP, although the correlation was statistically insignificant, p value more than 0.05.

Finally, we found 92.3% of patients are treated and 7.7% not treated which depends on platelet count and presence of clinical feature. In the first line treatment we found 93.1% of patients use Prednisolon induction due

to lower costs and greater availability compared with IVIG. In US, IVIG used for heavy bleeding because this can lead to faster rise in platelet counts than steroid but steroids used for children who do not respond to initial therapy with IVIG. (Grainger, 2017).

In the second line treatment which is indicated for patients with partially responds to first line treatment or platelet counts fall again after initial response, we found 31.8% of patients were on PRD maintenance and DAPSONE and 22.7 % use anti-D which is effectively used in RhD+ non splenectomized patients (Salama 1984).

In third line treatment we found 2 patients were on Nplate which is used in patients with chronic ITP who have had insufficient response to corticosteroid and immunoglobulins. Extensive studies have shown that Nplate can increase the platelet counts to safe levels in many patients with chronic ITP when the achievement occur in over than 90% of patients with short term response (Bussel et al. 2009; Bussel et al. 2016). Splenectomy done just for one patient, it may be due to failure or only an insufficient response to all other treatment modalities, with deterioration of his condition, or patient suffers from life threatening bleeding. (Ahmed et al. 2016; Davies, 2011).

CONCLUSION

1- Female patient with ITP more than male.
2- Most of the patients were in age range 2-10 years.
3- More than 80% of patients had no family history of immune thrombocytopenia.
4- About 70% of patients were sibling of consanguine father and mother.
5- Majority of patients presented with ecchymosis (91%) as a first symptoms appearance.
6- Most of patients used PRD induction as first line treatment, PRD maintenance and DAPSON mostly used as second line treatment and just three patients referred to third line treatment.

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