



## **Retrospective Evaluation of Chronic Idiopathic Thrombocytopenia in Libyan Children**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author HASE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors HASE and AIA managed the analyses of the study. Authors HASE and AIA managed the literature searches. Both authors read and approved the final manuscript.*

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### **ABSTRACT**

Immune thrombocytopenic purpura (ITP) is the most common cause of acquired thrombocytopenia in children. Approximately 10-20% of children with Immune thrombocytopenia (ITP) suffer from a chronic clinical disease that requires follow up and medical intervention according to the severity of bleeding manifestation.

**Aims:** To evaluate the demographic, clinical, and laboratory features, treatment modalities, and response to therapy in Libyan children with chronic idiopathic thrombocytopenia.

**Methods:** A retrospective study was conducted at the hematology clinic of the pediatric department, Benghazi medical center, and Benghazi Children Hospital. The duration of the study was from January 1998 to December 2018. comprised of demographics, clinical, laboratory data, therapy and therapy response in Libyan chronic ITP.

**Results:** In our study, the mean age of chronic ITP patients was 4.9 years, slightly higher in male patients 43 (52.4%) With a male/female ratio 1.1:1. The most frequent symptoms were mild which were limited to bruises and petechiae on the skin. (57.3%). The preceding history of viral infection was uncommon in patients with chronic ITP (22%) while the past history of MMR vaccination is

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quite rare and constituted only (2%). The mean platelet count before treatment (i.e. at presentation) was (22.7x10<sup>9</sup>/L) while mean platelet count after treatment (213.6 x10<sup>9</sup>/L. Treatment consisted of combined Steroid + IVIG in 27 (77.1% response), steroids in 23 (73.9% response), intravenous immunoglobulin (IVIG) in 11 (90.9% response), and no therapy in 21 (95.2% response). Complete response was achieved in 82.9% % showed a complete response either spontaneous or following the treatment. No patient was presented with intracranial hemorrhage.

**Conclusions:** Chronic ITP in Libyan children had a benign nature, none of our patients developed severe symptoms as life-threatening bleeding like CNS bleeding or died, IVIG give more optimistic response as compare to steroid. And the majority of children with chronic ITP in this study achieved remission.

*Keywords: Childhood; clinical profile; chronic; primary immune thrombocytopenia.*

## 1. INTRODUCTION

Primary immune thrombocytopenia (ITP) is one of the most common causes of symptomatic thrombocytopenia in children. It is an acquired hematological autoimmune disorder characterized by isolated thrombocytopenia (<100 × 10<sup>9</sup>/L) in the absence of secondary causes such as drugs, infections, malignancy, or secondary autoimmune diseases. The disease is caused by immunological platelet destruction as well as underproduction of \_ platelets in the bone marrow [1,2,3].

The diagnosis of primary ITP is based on the exclusion of other etiologies of thrombocytopenia. Immune thrombocytopenia mostly appears in a completely healthy child with variable bleeding manifestations ranging from cutaneous bleeding, such as petechial, purpura, and ecchymosis, Mucus membrane bleeding such as epistaxis, gingival bleeding, GIT bleeding, menorrhagia to Severe life-threatening intracranial hemorrhage (ICH). The intracranial hemorrhage is quite rare, occurring in 0.1- 0.5% of the children who have a history of head trauma and those patients have platelet count is less than 10× 10<sup>9</sup>/L [4,5].

Most of childhood \_ ITP cases carry an excellent outcome and recover completely. Only 10-20% of children develop chronic ITP which defined by the International working ITP group [3] as persistent thrombocytopenia (<100x10<sup>9</sup>/L) lasting more than 12 months [2].

Chronic ITP is \_ encountered mainly in older children, especially adolescent girls. Secondary causes such as systemic lupus erythematosus should be ruled out. Many of these children do not have any significant bleeding problems or require regular treatment. Patients with chronic ITP are clinically heterogeneous. Most of the

cases are mild and intermittent while \_ few have recurrent, severe bleeding. Some patients will have spontaneous, permanent remissions at some time during the course of the disease, and patients, will continue to have persistent thrombocytopenia [2,6].

The treatment in chronic ITP depends on bleeding severity, not on platelet count. Initial management or standard first-line treatment include either; observation alone, single or combination treatment with corticosteroids (prednisone, dexamethasone) and/or intravenous immunoglobulin (IVIg) or anti-D immunoglobulin [2,6].

The children with chronic ITP not responding to first-line therapy may benefit from the second-line treatment include splenectomy [6,7,8,9,10], Rituximab a chimeric monoclonal antibody (anti-CD20 [11,12] and the thrombopoietin (TPO) agonists TPO-RAs (Romiplostim and Eltrombopag) [13,14].

In children with ITP who have non-life-threatening mucosal bleeding and/or diminished health related quality of life (HRQoL) and Are not responding to first-line treatment, the ASH guideline panel suggests TPO-RAs as the best alternative therapeutic option then rituximab as a second option and lastly splenectomy [15].

The other second-line pharmacotherapy Include immunosuppressants; these drugs are used in case of first-line drugs failure or intolerance. These immunosuppressants comprise Azathioprine, cyclophosphamide, and cyclosporine are the main drugs in use. Danazol, dapsone, mycophenolate mofetil, and vinca alkaloids are a few other second-line drugs with unproven efficacy, and these are used rarely in children [15,16,17].

Fifty percent of chronic ITP children get spontaneous recovery within 5 years of diagnosis [16] and in few children even many years later [17].

## 2. MATERIALS AND METHODS

This retrospective study included all diagnosed children of chronic primary immune thrombocytopenia followed up in the pediatric hematology clinic at Benghazi medical center and Benghazi Pediatric hospital from January 1998 to December 2018. All case files were evaluated for demographic features, history, clinical examination, platelet count, therapy received, and response to treatment. All children with secondary causes of thrombocytopenia were excluded from the study population.

### 2.1 The Diagnosis of Chronic ITP

The diagnosis of chronic ITP according to the following Definitions and terminologies [2] Chronic ITP: primary immune thrombocytopenia lasting for more than 12 months.

### 2.2 The Clinical Profile Evaluation

The clinical profile evaluation including history, age (1-16 years), the gender, complaints, and preceding history of infection, and past MMR vaccination were recorded. Physical examination and platelet count at presentation and after treatment were recorded

### 2.3 Assessment of Bleeding

Bleeding severity was assessed at this study using a modification of the scoring system of Bolton-Meggs and Moon. The Bolton-Meggs and Moon arbitrarily divided bleeding signs into four categories:

**None:** Asymptomatic.

**Mild:** Bruising and petechiae; occasional minor epistaxis, very little or no interference with daily living.

**Moderate:** More severe skin manifestations with some mucosal lesions; more troublesome epistaxis and menorrhagia.

**Severe:** Bleeding episodes (epistaxis, melena, and/or menorrhagia) requiring hospital admission and/or blood transfusion;

symptoms seriously interfering with the quality of life, suspected or documented intracranial hemorrhage (ICH), and other life-threatening or fatal hemorrhage at any site.

Regarding the bleeding severity because none of our patients develop severe bleeding so only compare mild with moderate bleeding symptoms.

Platelet count before treatment starting (i.e. at presentation) and after treatment starting as a therapy response also included in Chronic ITP profile evaluation.

### 2.4 Treatment Options

Treatment options received by children under study with chronic ITP include: A-First Line Treatment as the following:

1. Only observation (no pharmacological treatment).
2. Steroids. Prednisolone 1-2 mg/kg/day for 2wks than tapered for next week if patient show response or developed steroid toxicity [10].
3. Intravenous Immuno-Globulin (IVIG); 0.8-1 g/kg for 1-2 days Intravenous infusion [10]
4. Combined IVIG plus prednisolone. While anti-D treatment not used in our study group and because none of our patients had severe bleeding so none of them is a candidate to the second line of therapy.

### 2.5 Response to Therapy

Response to therapy Defined as follows:

- I. A complete response (CR) was defined as a return to normal platelet count (greater than  $150 \times 10^9/L$ ) during or after therapy.
- II. A partial remission (PR) was defined as an increase in the platelet count to greater than  $50 \times 10^9/L$ .
- III. No response (NR) was defined as no response to therapy with a continued platelet count below  $50 \times 10^9/L$ . [23]

### 2.6 Statistical Analyses

The studied cases were entered in Microsoft Excel spreadsheet and analyzed by statistical methods and P-value was used to find the significance and value of  $p < 0.05$  was defined as a statistically significant difference. The statistical packages used are SPSS 18 for the Fischer's Exact test and Paired Samples test.

### 3. RESULTS

In this retrospective study, a total of 82 patients diagnosed as chronic ITP was studied. The demographic, Clinical profile, laboratory data, treatment option, and response were analyzed.

#### 3.1 Demographic Profile

Children between 1 - 5 years comprise 62.6% (n=57) of the study population and the mean age of the patients was 4.9 years. Males constitute 52.4% (n=43) of the study population with male: female ratio 1.1:1.

The preceding history of viral infection was uncommon in patients with chronic ITP (22%) while the past history of MMR vaccination is quite rare and constituted only (2%).

#### 3.2 Clinical Presentations

57.3% (n=47) of children had mild symptoms followed by those showing moderate symptoms 42.7% (n=35) which was not a statistically significant result ( $P = .18$ ) among age groups. None of our patients exhibited severe bleeding symptoms.

#### 3.3 Laboratory Profile

There was a significant statistical difference in the average of platelet counts between before treatment and after the treatment ( $P = .000$ ), The mean platelets count at presentation was ( $22.7 \times 10^9/l$ ) while the mean Platelet counts after the treatment were  $213.6 \times 10^9/L$ ; as shown in Table 1.

**Table 1. Demographic, clinical and laboratory characteristics of chronic ITP study population (n = 82)**

<b>Age at diagnosis (years) Mean ±SD</b>	<b>4.9 years ± SD (3.26)</b>
<b>Age</b>	<b>No. (%)</b>
1-5 years	57(62.6)
6-10 years	18 (19.8)
>10 years (11-16 years)	7 ( 7.7)
<b>Gender</b>	
Male	43 ( 52.4)
Female	39 (47.5)
<b>Previous infection</b>	
Yes	18 (19.8)
No	64 (70.3)
<b>Previous MMR vaccination</b>	
Yes	1 (1.1)
No	81( 98.9)
<b>Bleeding severity</b>	
Mild	47 (57.3)
Moderate	36 (42.7)
Severe	0 ( 0)
<b>Platelet counts Mean ± SD</b>	
Before treatment	$22.7 \times 10^9/L \pm 21.88$
After treatment	$213.6 \times 10^9/L \pm 140.26$

MMR : measles,mumps,rubella .SD: standard deviation

**Table 2. Treatment modalities and response to different treatment modalities in chronic ITP**

Type of Treatment	No.( % )	Response		
		Complete	Partial	None
No T/T	21 ( 25.7)	20 (95.2%)	1 (4.8)	0
Steroids (one or more courses)	23 (28.0)	17 (74.0%)	3 (13.0 %)	3 (13.0 %)
IVIG	11 ( 13.4)	10 (91.0%)	1 (9.0)	0
Steroid + IVIG	27 ( 32.9)	21 (78%)	3 (11%)	3 (11%)

IVIG: Intravenous Immunoglobulin

### 3.4 Treatment Option and Treatment Response

A-First line treatment including:

- I. **Observation only** (No treatment): Twenty-one patients did not receive any treatment; Out of 21 patients 20(95.2%) showed complete response while 1 (4.8%) patient exhibited a partial response.
- II. **Steroids therapy:** Twenty-three patients received one or more courses of steroid; the complete response was achieved in 17 (74%) patients while no response in 3 (13%) patients and there were partial responses in 3 (13%) patients.
- III. **IVIG:** Used for 11 patients, 10 (91%) patients showed complete response, and 1 (9%) partial response.
- IV. **Steroid + IVIG:** Out of 27(77.7%) patients who received combined therapy of steroid and IVIG,21 (25.6%) showed a complete response, 3(11%) showed partial response while another 3( 11%)did not show any response.

### 3.5 Overall Response

Final response: The majority of the patients were complete response 68 (82.9%)of the patients, the partial response was 8 (9.8%)of the patients, and no response was 6 (7.3%) of the patients; as shown in Table 3.

**Table 3. Over all response**

Response	NO.	%
CR	68	82.9
PR	8	9.8
NR	6	7.3

*CR; complete response, PR; partial response, NR; no response*

75% of our study group received treatment during follow up, with complete response achieved in 82.9% of the patients either spontaneous or after received treatment.

## 4. DISCUSSION

The basic aim of this retrospective study was to evaluate the demographic, clinical, laboratory profile, the therapy modality as well as their response to various received treatment of chronic ITP children in a developing country like Libya.

Although the precise number of chronic immune thrombocytopenia is not easy to estimate because of the benign nature of the disease which is mainly manifested as mild cases and no follow up is done at the hematology clinic.

The finding of only 82 cases of chronic ITP over 20 years indicates that the chronic ITP is quite rare in Benghazi in contrast with that reported as the frequency of chronic ITP in children is between 25% to 31% in the literature [18-19].

In this study, the most common age group was 1-5 years accounting for 62.6% of the study population with the mean age of patients at diagnosis was 4.9 years which is similar to various studies [20-21]. Male and female children constituted 52.4 % and 47.5% respectively, with male to female ratio1.1:1. There was no significant gender difference the same as in one study [22] in contrast to other studies which showed; slight female predominance [23,24,25].

As compared to the Arabic population the reports from Lebanon [26] and Arabian Gulf region [27] have shown that the majority 80% of patients with chronic ITP were males while more frequent in Egyptian females [28].

The preceding history of viral infection was uncommon in our patients with chronic ITP (22%) while the past history of MMR vaccination is quite rare and constituted only (2%).as international data chronic ITP usually not preceded by a viral infection, two studies in china demonstrated the history of viral illness insignificant % of the patients [33,34] while A history of preceding viral infection was common in chronic ITP cases (63%.) [27].

### 4.1 Clinical Profile

In 82 Libyan children with chronic ITP, the most common presentation was mild symptoms (petechiae and purpura (57.3%) followed by moderate one (42.7%) which is in concordance with other studies as [29] in which the common presentation signs were skin bleeding alone in 41 (68.3%) patients followed by skin and mucous membrane in 17 patients (28.2%) which was same as observed in studies(21, 30) [21,30] The majority of children had mild bleeding symptoms.

No definitive statistical difference was found between the type of bleeding also there was an absence of intracranial bleeding in our study group as reported in other studies [29,30].

This might simply be a reflection of the benign behavior of the chronic ITP as reported in the study by Glanz J which showed cutaneous bleeding in 52/60 (88%) patients, mucosal in 9/60 (23%) patients and no patient got internal bleeding in the study conducted by Kühne T study showed more aggressive presentations in the study conducted by Asian and European groups of children [31]. Four cases of ICH were identified among children with chronic ITP over a period of 10 years in five Egyptian centers.[32]While in china study [21]show Intracranial hemorrhage (ICH) occurred in two children (0.4%).

In our study, there was a significant statistical difference in the average of platelet counts between before treatment and after the treatment ( $p = .000$ ), this indicated a good response to different used treatments.

All patients in our study received only first-line therapy either observation alone or pharmacological therapy including (prednisolone, IVIG, alone or in combination which is not uniform the same as the management of ITP in children in the other Arab countries. It ranges from observation, medical treatment depending on bleeding symptoms, acceptable platelet counts, and availability of hospitalization or outpatient treatment [35,36].

#### **4.2 Treatment Modality in Our Chronic ITP Patient**

Generally, 3/4 of our study group received first-line pharmacological therapy while the remaining 1/4 kept in observation alone [Table1].

Nearly one-third (32.9%) of the patients were receiving both intravenous immunoglobulin (IVIG) and steroid (32.9%) followed by steroids alone (28%), observation (25.7%), and lastly IVIG (13.4%)

No patient received the second line of therapy. These data confirm that chronic ITP in childhood runs a benign course and may remit over a variable period. Therefore, the therapeutic intervention has to be individualized, and the second line therapy which is not always safe must be restricted to severe or refractory cases. In contrast to the study conducted by China [13], The most widely used treatment for children was intravenous immunoglobulin (IVIG) (61.9%) followed by steroids+ IVIG (15.9%), anti-Rh(D)

immunoglobulin (9.5%), rituximab and splenectomy (1.6% each).

#### **4.3 Response during the Chronic Phase**

In the current study although the complete response (CR) rate obtained with observation alone constitute (95.2%) which is higher than that with various pharmacological therapy.

The response to a single course of IVIG in our study was more optimistic 10 (90.9%) than to the steroid response (73.9%). Although Steroid provides a cheaper alternative to IVIG in countries with poor supply, Wong and Aronis [24,34] show a lower response of (14.3%.&38.5%) after variable courses of IVIG. In our study the complete response (CR) to steroids was 73.9% which is higher than reported in other studies [24,36].

#### **4.4 Overall Outcome**

In our study, there was only 6(7.3%) non-responder patients, it is not in agreement with a study by Glanz et al. (2008) which found the non-responder higher [28].

None of our patients had CNS bleeding or died from any bleeding during the period of following. As compared to other Arabic world the mortality rate of ITP is very low in Arab countries, matching the international standards of less than 1%. Death was due to ICH in one case in the Emirates study [38], two children in the Egyptian study [32] and one patient in a report from Tunisia [39].

In our study from a total 82 subjects, 82.9% (68) of children had complete response irrespective of whether they had been managed by observation only or had received the first line pharmacological therapy. These facts supported that ITP is a benign condition for most affected children as reported in literature.

### **5. CONCLUSION**

Chronic ITP in Libyan children had a benign nature, none of our patients develop severe symptoms of life-threatening bleeding like CNS bleeding or death. IVIG gives more optimistic response as compared to steroid and the majority of children with chronic ITP in this study achieved remission. The majority of patients with ITP received treatment although may not require

any intervention while the minority of children kept in observation.

## 6. RECOMMENDATION

This study recommends that standardization of practical guidelines for management of ITP in Libya should be established to improve the current practices and the safe management of chronic ITP.

More research with a larger sample size is required to study the incidence and outcome in the Libyan population after application of standardized practical guidelines for management of ITP in our country is needed.

## CONSENT

All respondents' parents who agreed to participate in the study were required to initialize the informed consent form.

## ETHICAL APPROVAL

The principle of Medical Research Ethics guidelines from the Faculty of Medicine, University of Benghazi, were observed during this study.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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