Clinical profile and outcome of newly diagnosed immune thrombocytopenic purpura among Yemeni children aged less than 15 years

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Introduction
Immune thrombocytopenia purpura (ITP) is an acquired primary immune-mediated disease by a transient or persistent isolated decrease of the platelet count associated with impaired or suboptimal platelet production with an increased risk of bleeding. ITP is defined as a platelet count (<100 × 10^9/l) in the absence of other secondary causes. Newly diagnosed ITP is an ITP with a duration less than 3 months.

Objective
The objective of the study was to assess the clinical profile, laboratory findings, management options, and outcome of newly diagnosed ITP among Yemeni children aged less than 15 years.

Patients and methods
A prospective observational study was carried out between January 2013 and December 2020 at Al-Mukalla Maternity and Children Hospital and University Hospital for Mother and Child Health along with cases seen by the authors at the private clinic in Al-Mukalla city/ Hadhramout Governorate/Yemen. The study included children aged more than 6 months to less than 15 years with newly diagnosed ITP.

Results
This study includes 36 children, 21 males and 15 females, the ages range from 1 year and 8 months to 13 years. The mean ± SD (range) age is 4.23 ± 2.41 years. The most common presentation of ITP was cutaneous bleeding that is found in 100% of cases. About 66.7% have platelet count at the time of diagnosis between less than 20 and 10 × 10^9/l. About 42.3% of patients who underwent observation method (no treatment) have complete remission. About 77.8% of cases achieve complete response after treatment.

Conclusion
The outcome of newly diagnosed ITP is more favorable when it occurs at young-age children less than 3 years, while sex difference do not affect outcome.

Keywords:
children, newly diagnosed immune thrombocytopenia purpura, Yemen

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Introduction

Immune thrombocytopenia purpura (ITP) is an acquired primary immune-mediated disease characterized by a transient or persistent isolated decrease of the platelet count associated with impaired platelet production with an increased risk of bleeding. The International Working Group defines ITP as a platelet count (<100 × 10^9/l) in the absence of other secondary causes [1–3]. In children, ITP often resolves spontaneously or following therapy within 6–12 months of diagnosis [4]. Several studies have estimated the annual incidence to be between 1 and 6.4 cases per 100 000 children [2,5,6]. ITP can affect any age, but there is a peak incidence between 2 and 5 years [7,8], and characterized by a variety of skin and mucous-membrane-bleeding manifestations [9]. ITP is classified based on duration into newly diagnosed less than 3 months, persistent (3–<12 months), and chronic (≥12 months) [10,11]. The goal of therapy is to cease any active bleeding and prevent future hemorrhage [1,3].

The aim of the study was to assess the clinical profile, laboratory findings, management options, and outcome of newly diagnosed ITP among Yemeni children aged less than 15 years.

Patients and methods

Study design and setting

A prospective cross-sectional observational study was carried out between January 2013 and December 2020

at Al-Mukalla Maternity and Children Hospital and University Hospital for Mother and Child Health, including all cases of ITP along with cases seen by the authors at the private clinic, in Al-Mukalla City/Hadhramout Governorate/Yemen.

Inclusion criteria

(1) Age more than 6 months and less than 15 years.
(2) Newly diagnosed ITP who does not receive any treatment within 2 weeks.
(3) Approval by parents or caregivers.

Exclusion criteria

(1) If the child was exposed to a platelet-depleting medication (such as antiepileptics and sulfonamide antibiotics) in 6 weeks before diagnosis.
(2) Child with secondary ITP.
(3) Patients with incomplete clinical data.
(4) Patients with losing follow-up.

Definitions

(1) Complete response (CR) was defined as platelet count more than 100×10^9/l and persists for at least 6 weeks.
(2) Response (previously named 'partial response') was defined as platelet count between 30 and 100×10^9/l or doubling of the baseline count.
(3) No response: any platelet count less than 30×10^9/l or less than doubling of the baseline count was described [2,12].

All cases included in the research were subjected to the following:

(1) Detailed history taking, including age, sex, positive consanguineous marriage, any drug intake within 6 weeks before onset, history of vaccination within 4 weeks of onset, and positive history of preceding viral upper respiratory tract infection within 4 weeks of onset, particular emphasis was paid to symptoms of bleeding tendencies.
(2) A complete physical and systemic examination was conducted and all clinical data were collected, especially including the presence and distribution of bleeding manifestations.
(3) Investigations done include the following: complete blood-count examination of the peripheral-blood smear. Bone marrow aspiration was done to all cases. Other investigations like ANA, stool for *Heliobacter pylori* antigen, HBsAg, HCV antibody, and HIV antibodies were done when indicated. Antiplatelet–antibody test was not done for the patients in the study because it is not available in Yemen and also because it is not essential for diagnosis [13,14].

Platelet count was done at initial diagnosis and weekly till response, then every month till 3 months. Management option was either observation given to children with minor bleeding symptoms with platelet count of 20–30×10^9/l, then followed closely, and received treatment on demand [15,16], or steroid treatment in the form of oral prednisone at 2 mg/kg/day (divided doses) for 2–4 weeks and then tapered. If no response or partial response, we shift to intravenous immunoglobulin G at a dose of 0.4–0.8 g/kg/dose for 5 days, if no improvement, shifting to a combination with steroid. Platelet transfusion is given at any time where life-threatening bleeding was expected [17]. Anti-D and other modes of treatment like rituximab were not given.

Ethical consent

(1) The study protocol was conducted according to principles of the Declaration of Helsinki, as well as reviewed and approved by the Ethical Research Committee at Hadhramout University/College of Medicine.
(2) The authors explained the steps and value of the research, including management options, complications, and outcome of the disease to all eligible participants. Those who agreed to be included in the study signed a fully informed consent.

Statistical methods

The data were processed and analyzed by using computer, and the data were analyzed by proportion and percentage. A *P* value less than 0.05 was considered significant.

Results

This study includes 36 children, 21 males and 15 females, the ages range from 1 year and 8 months to 13 years. The mean ± SD (range) age is 4.23 ± 2.41 years.

The majority of cases 86% have abrupt onset less than 2 weeks. There are no cases of positive family history of ITP or bleeding tendency, positive consanguineous marriage occurs in 19% of cases. There is no hepatosplenomegaly nor generalized lymphadenopathy, the most common presentation of ITP was cutaneous bleeding only (petichae, purpura, and ecchymosis) that is found in 100% of cases. There is only one case that has bloody diarrhea. There is no hematemesis. There are no cases of intracranial hemorrhage (ICH) or genitourinary bleeding. Rest of the findings are shown in Tables 1 and 2.

Regarding the relation between bleeding manifestations and age, there is weak statistical difference ($P = 0.049$) (Table 3).

There is statistical difference regarding the relation between bleeding manifestations and sex (P = 0.028), indicating increased incidence of nasal bleeding and other noncutaneous bleeding with females than males (Table 4).

Table 4 shows the laboratory features at the time of diagnosis, where 66.7% have platelet count less than 20–10 × 10^9/l. There are eight cases that are anemic in association with ITP, but the cause was iron-deficiency anemia, also, nine cases are associated with abnormal white blood cell count in the form of leukocytosis that may be in association with secondary bacterial infection.

Table 5 shows the response following different treatment methods, where about seven cases undergo the observation method, of them, about three (42.3%) have CR, while one case has response, and three cases have no response.

The group that undergoes treatment includes 33 cases where 29 cases have treatment from the beginning plus four cases from the observation group, where one case has response and three cases no response.

The treatment group is divided into three lines where the first line with oral corticosteroids (prednisolone); therefore, 33 cases undergo treatment method first with oral steroids, about 19 cases achieve CR, five have response, and nine are resistant.

There are 14 cases that had received intravenous immunoglobulin, of whom about six have remission and eight are resistant. The resistant cases had received combination treatment of intravenous immunoglobulin and steroids, of whom three patients have response and five cases are also resistant.

Regarding the outcome of patients, where about 28 (77.8%) have CR, and three (11.1%) for response and five cases have no response. There are no mortality cases in our study (Fig. 1).

Regarding the relation between response to age and sex, there is statistical significance with P value of 0.011 to age where all children less than 3 years achieve CR, while there is no statistical significance regarding sex (P = 0.694) (Table 6).

Table 1 Personal data and clinical features of immune thrombocytopenia purpura at the time of diagnosis (*n*=36)

Items	*n*=36 [*n* (%)]
Personal data	
Age (years)	
<3	15 (41.7)
≥3	21 (58.3)
Mean±SD (range)	4.23±2.41 (1.5-12.4)
Sex	
Male	21 (58.3)
Female	15 (41.7)
Clinical features	
Onset	
Abrupt	31 (86.1)
Insidious	5 (13.9)
Positive consanguineous marriage	7 (19.4)
Preceding history of viral URTI	12 (33.3)
History of vaccination	1 (2.8)
Fever	6 (16.7)
General weakness	8 (22.2)
Joint or bone pains	5 (13.9)
Pallor	8 (22.2)
Bleeding manifestations	
Cutaneous bleeding	36 (100)
Nasal bleeding**	14 (38.9)
Gingival bleeding**	6 (16.7)
GIT bleeding**	1 (2.8)

GIT, gastrointestinal tract; URTI, upper respiratory tract infection.
**More than one type.

Table 2 Relation between bleeding manifestations and age

Bleeding manifestations	Age (years) [*n* (%)]		*P*
	<3	≥3	
Cutaneous bleeding	15 (100.0)	21 (100.0)	–
Nasal bleeding†	3 (20.0)	11 (52.4)	0.049*
Gingival bleeding§	1 (6.7)	5 (23.8)	0.367
GIT bleeding§	0	1 (4.8)	1.000

†χ^2 test. §Fisher exact test. *Statistical significant difference (P<0.05).

Table 3 Relation between bleeding manifestations and sex

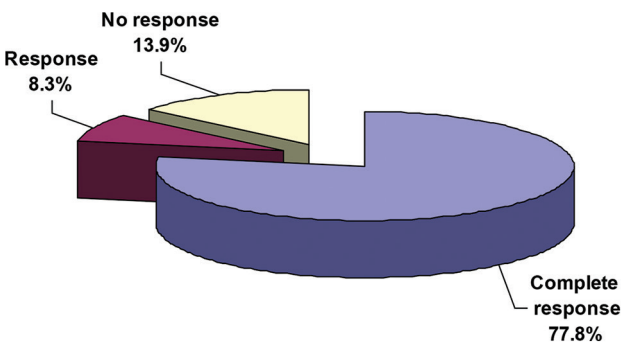
Bleeding manifestations	Sex [*n* (%)]		*P*
	Male	Female	
Cutaneous bleeding	21 (100.0)	15 (100.0)	–
Nasal bleeding†	5 (23.8)	9 (60.0)	0.028*
Gingival bleeding§	3 (14.3)	3 (20.0)	0.677
GIT bleeding§	0	1 (6.7)	0.417

†χ^2 test. §Fisher exact test. *Statistical significant difference (P<0.05).

Discussion

This study includes 36 children, they were 21 males and 15 females. These cases occur during 8 years with

Figure 1



Outcome of patients.

Table 4 Laboratory features at the time of diagnosis (*n*=36)

Laboratory features	Frequency	%
Platelet count ($\times 10^9$/l)		
>20-40	9	25
<20-10	24	66.7
<10	3	8.3
Hemoglobin		
Normal	28	77.8
Abnormal	8	22.2
White blood cells		
Normal	27	75
Abnormal	9	25

Table 5 Response following different treatment methods (*n*=36)

	n (%)
Response following no treatment method (*n*=7)	
Complete response	3 (8.3)
Response	1 (2.8)
No response	3 (8.3)
On treatment	29 (80.6)
Response following steroid treatment (*n*=33)	
Complete response	19 (57.6)
Response	5 (15.2)
No response	9 (27.3)
Response following IVIG treatment (*n*=14)	
Complete response	6 (42.9)
Response	0
No response	8 (57.1)
Response following combination of steroid and IVIG treatment (*n*=8)	
Complete response	0
Response	3 (37.5)
No response	5 (62.5)

IVIG, intravenous immunoglobulin G.

Table 6 Relation between response to age and sex (*n*=36)

Personal data	Complete response (*n*=28)	Partial/no response (*n*=8)	*P*
Age (years)			0.011*
<3	15 (100.0)	0	
≥3	13 (61.9)	8 (38.1)	
Sex			0.694
Male	17 (81.0)	4 (19.0)	
Female	11 (73.3)	4 (26.7)	

Fisher exact test. *Statistical significant difference (P<0.05).

an average of 3–6 new cases per 100 000 years, with a population of Al-Mukalla about 285 132, about 46% of them are children less than 14 years [18]. This is in agreement with the incidence of ITP in literatures that is about 3–10 per 100 000 children per year below 16 years of age [7,11,19].

The mean ± SD age is 4.23 ± 2.41 years with 41.7% of cases that occur in children less than 3 years, this is comparable with the results reported by literatures [14,20,21], who observed a higher incidence of the disease in children aged 2–4 years. Probably, this age group is more likely to expose to viral illnesses and vaccination.

The male-to-female ratio was 1.4:1 with slight predominance (58.3%) of males over females. Males and females seem equally affected as reported by most studies. However, male predominance has also been reported in children less than 2 years of age, probably being a male is a risk factor [14,15,22–24].

In our study, about 86% of cases of acute ITP have recent onset less than 2 weeks, this pattern is consistent with the acute as reported by Makis *et al.* [25], where about 91% of cases of newly diagnosed/persistent form have abrupt onset.

Positive consanguineous marriage was observed in 19.4% of families, consanguinity is widely distributed in Yemen, which may have contribution to genetic diseases [26–28].

In our study, only 33.3% of cases report preceding viral infection, which is a common finding in ITP to occur after many types of vaccine-preventable diseases [29–34]. Blanchette and Bolton-Maggs [35] reported preceding viral infection in about two-thirds of ITP cases. The lower percentage may be due to hot and warm climate at the study area, Mukalla city, where the duration of winter is short throughout the year.

There is only one case-reported history of vaccination within 4 weeks of onset, and it was the polio-booster doses as given by the vaccination campaign. Because vaccines are designed to induce an immune response that mimics natural infection to produce immunologic protection, it is theoretically possible that vaccines besides could trigger ITP [27,36,37].

The most common presentation of ITP was cutaneous bleeding that is found in 100% of cases, similar results are observed [38,39].

In this study, a weak statistical difference (P = 0.049) was found with severity of bleeding manifestations and increasing age, indicating increased incidence of nasal bleeding and other noncutaneous bleeding in children more than 3 years, similar results were observed in previous studies [4,23]. There are no cases of genitourinary bleeding in the form of hematuria and no cases of conjunctival bleeding, no cases of ICH in our study.

Bleeding manifestations in patients with ITP range from mild skin bruises to life-threatening ICH. Severe bleeding occurs when the platelet count falls less than 10 × 10^9/l [9,40]. ICH is a well-recognized complication of ITP and has been reported to occur in less than 1–2% of patients [41,42]. In this study, 66.7% of patients have platelet count less than 20–10 × 10^9/l.

It was found in our study that the minimum platelet count for the bleeding manifestation to appear is 40×10^9/l, similar results are in accordance with other studies [38,39].

In this study, seven of 36 cases undergo the observation method, three (42.3%) have successful complete remission, while one case has response, and three cases have no response.

A study conducted by Akbayram *et al.* [43], reveals observation success rate of 69.2%, while other studies show a lower success rate with as low as 12.9, 5.8% [39,44], the less number of cases undergo the observation method due to risk of hemorrhage and also due to consent form that allows patient's family in charge to refuse observation method. According to American Society of Hematology 2019 guidelines [3] and Updated International Consensus Report recommendation for children with newly diagnosed ITP and a platelet count of less than 20×10^9/l, who have no or mild bleeding (skin manifestations) only, is observation, regardless of the platelet count [10].

The group that undergoes treatment with steroids includes 33 cases, where about 19 (57.6%) have CR, five (15.2%) have response, and nine (27.3%) no response, higher percentages of CR 81.2% are shown with other studies that used methylprednisolone, the lower results in our study because we use oral steroids and may be due to compliance problems in children, in contradiction to i.v methylprednisolone [44].

In a study conducted in Iran, using different modalities for treatment of primary ITP, they found a CR of 51.87% by using parenteral corticosteroids, 16.04% by using oral corticosteroids, and 24.06% by using both corticosteroids + intravenous immunoglobulin G [45]. For children who present with bleeding and/or diminished health-related quality of life, the treatment recommendation is prednisolone, traditional first-line therapy is oral corticosteroids. Many guidelines recommend limiting the use of corticosteroids to a maximum of 6–8 weeks, including the treatment dosing and taper, because higher dose given over a longer period may be harmful [3,10].

In our study, 14 cases who have either response or no response received intravenous immunoglobulin, of whom about six patients have remission, and eight are resistant. Then, eight patients undergo combination treatment with steroids and intravenous immunoglobulin with three (37.5%) that had response and five (62.5%) had no response with no remission cases.

Regarding outcome, 28 (77.8%) have CR, 3 (8.3%) response, and five (13.9%) no response. There is statistical significance (P = 0.011) to age where all children less than 3 years achieve CR, therefore, the prognosis of newly diagnosed ITP is more favorable when it occurs at young-age children less than 3 years, while no statistical significance regarding sex (P = 0.694) difference does not affect outcome, this is in agreement with several studies [2,4,23,27,43,44].

Conclusions and recommendations

(1) The outcome of newly diagnosed ITP is more favorable when it occurs at young-age children less than 3 years, while sex difference does not affect outcome.

Limitations of our study

(1) Low sample of the study, despite extended period, probably because of low population at Al-Mukalla city, and may be due to dropout of cases not present to us that may have traveled to other centers in Aden or Sanaa.
(2) We cannot extend the period of observation beyond 3 months to identify the persistent and chronic cases, as the level of education for most families is low.
(3) There are cases excluded from the study because they are even not complete after 3 months of follow-up.
(4) We cannot include too much cases in the observation as the ethical committee allows families enrolled in the study to stop the observation strategy.
(5) We did not include much cases with treatment of intravenous immunoglobulin because it is too much expensive.

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Conflicts of interest

There are no conflicts of interest.

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