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ORIGINAL RESEARCH

Clinical Profile of Immune Thrombocytopenic Purpura in Paediatric age Group

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ABSTRACT

Background: Platelets play a vital role in hemostasis. Idiopathic / Immune thrombocytopenic purpura (ITP) is a common bleeding disorder in children, where autoantibodies mediated consumption of the platelets, suppression of platelet production by bone marrow megakaryocytes leads to thrombocytopenia and bleeding manifestations. Incidence is 6.4 per 10000 among children and 3.3 per 10000 adults per year.1 There is highest male to female ratio in infancy and it decreases with older age groupchildren. No significant seasonal variation. Vaccination may play an important role in the etiology of ITP in infants. History of a preceding viral infection 1-6 weeks before the onset disease is present in 60% of cases. Bone. narrow was routinely performed but evidences confirmedthat its rarely needed at presentation, must be considered if having severe bleeding or not responding to treatment.

Materials &Methods:Details about children with ITP who presented to our hospital between October 2020 and August 2021 were collected using a proforma. The study was designed as a cross-sectional study. To meet the sample size, convenience sampling was used.

Results: Total number of children recruited with a clinical diagnosis of primary itp was 120 after excluding the ones which had a secondary cause identified, the total primary itp studied were 100. among them based on the duration of symptoms (as per definitions) they were categorized into newly diagnosed, persistent and chronic itp. There were 46 cases of chronic itp and 44 cases of persistent ITP. 73 percent of all patients were between the ages of 1 and 10 years. in total, 8.9 percent of them had severe bleeds. there was no link discovered between bleeding and platelet count. a high nordic score (10-14) had a high predictability for short-term symptoms.

Conclusion: In our study, there was a higher incidence of its presenting in the hospital. Higher a percentage of them had severe bleeding.

Keywords: Immune thrombocytopenia, bleeding, nordic score, platelet, fatal clinical haemorrhages.

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INTRODUCTION

Platelets also called as thrombocytes are the critical factors in controlling the bleeding disorders, initiating and maintaining haemostasis. Immune Thrombocytopenia (ITP) is an acquired autoimmune, hematological disorder. characterized by isolated thrombocytopenia (peripheral blood platelet count <100x109⁄ l) in the absence of other causative systemic disorders.[1,2] The pathogenesis of ITP remains incompletely understood. The underlying mechanism is thought to be the reduced lifespan of platelets due to antibodies-mediated

accelerated destruction by the reticuloendothelial system and abnormal production by bone marrow.[2,3] Bleeding resulting from platelet disorders is characterized by bleeding into the skin and mucosal membranes and prolonged bleeding, following trauma.[4] More than 80% of diagnosed children, if left untreated, may undergo spontaneous remission with complete recovery of platelet count within 2-8 weeks.[5]Patients presenting with no bleed or mild bleed (defined as skin manifestations only, such as bruising and petechiae) are managed with observation alone irrespective of platelet count.[1] Risk of severe hemorrhage and intracranial bleed is about 3% and less than 1% respectively.[5,6] In all cases with clinically significant bleed, treatment aim to achieve adequate hemostasis and not the normal platelet count. First line drugs therapy includes oral corticosteroids (2mg/kg/day) for two weeks followed by tapering over one week or intravenous methylprednisolone (30mg/kg for 3 days) or a single dose of intravenous immunoglobulin (IVIG) (0.8-1g/kg) or intravenous Rhesus anti-D (50-75 ug/kg).[1] Immune thrombocytopenic purpura (ITP) is an autoimmune bleeding illness that manifests itself in children as petechiae, easy bruising, and mucosal bleeding, among other symptoms.[1] Thrombocytopenia isolated (platelet count 100,000/ul with normal white blood cell count and haemoglobin) is a condition defined by isolated thrombocytopenia.[1-3] Immune thrombocytopenia is caused by platelet antibodies, which cause platelet breakdown to occur more quickly and impede platelet synthesis. The majority of cases are classified as primary (hereinafter referred to as ITP), while the remainder are attributed to comorbid disorders (secondary ITP).

This classification implies that ITP is a clinical pathologic entity with a single aetiology. But the heterogeneity in natural history and responsiveness to therapy suggests that ITP is composed of a number of different illnesses that result in the generation of platelet autoantibodies as a result of the disease. According to findings from secondary forms (such as coexisting immunological deficiency and molecular mimicry after infection), platelet-reactive antibodies are produced by a variety of processes, all of which are discussed in this paper. Platelet turnover, bleeding tendency, and response to ITP-directed therapy are all aspects that may be influenced by environmental and genetic factors.[4]

ITP can affect people of all ages, however the highest incidence occurs between the ages of 2 and 5 years. Incidence of childhood ITP is predicted to be 4.0 - 5.3 children in per 100,000 children.[2] The incidence of paediatric ITP is significantly higher than the incidence of adult ITP. There is no sex prediction in children with ITP, albeit it is more common in boys than in girls in babies and toddlers.[6]

When it comes to children, the diagnosis of ITP is primarily one of exclusion. The child is typically one to seven years old, has skin or mucosal bleeding, is generally healthy, and does not have lymphadenopathy or organomegaly at the time of the occurrence. Unusually low haemoglobin (Hb) levels, normal white blood count (WBC), and normal peripheral blood smear are found in an isolated thrombocytopenia, which is confirmed by a full blood count. Children with newly diagnosed childhood ITP can be managed in a variety of ways, including observation, the use of intravenous immunoglobulin (IVIG), steroids, and anti-D immunoglobulin, either alone or in combinationThrombopoietin, Rituximab, and/or splenectomy may be beneficial for children who develop chronic ITP.[7-14]

This study examines the varied clinical presentations of ITP, emphasising the significant variations between acute and chronic ITP in terms of their presentation and degree of bleeding, as well as the need of early diagnosis. This study contributes to the current body of knowledge on ITP and gives useful information about the applicability of the Nordic score in predicting the likelihood of a newly diagnosed ITP progressing to chronicity and how to predict it.

Objectives: Primary Objective:

1. To study the clinical profile of children presenting with Immune thrombocytopenic purpura.
2. Proportion of children presenting with moderate to severe bleeding in immune thrombocytopenic purpura at their first presentation.

Secondary objectives:

1. The relationship with platelet counts and severity of bleeding.
2. The prediction of duration of ITP based on NORDIC scoring system.

MATERIALS & METHODS

Study period – 2years, October2020-August2021
Study design – Prospective, observational study
Study setting – Pediatrics OPD/ wards/ PICU, Katuri Medical College, Guntur
Inclusion criteria – All children between 1-18 yrs with a clinical diagnosis of primaryImmune Thrombocytopenic purpura (ITP).
Exclusion criteria- Secondary causes of Immune thrombocytopenia as evaluated by theprimary clinician.

Sampling:

Sampling is done by convenience to meet the sample size in the study duration.The study was done on basis of convenience sampling.
All children 1-18 years of age with a clinical diagnosis of ITP made by the treating team, seen at St John's medical college hospital OPD/IPD were included in the study.
A structured proforma was used to collect data about the demographic details, clinical details of this presentation, clinical details of their first presentation, nature and severity of bleeding and relevant clinical examination and laboratory parameters. For the children newly diagnosed with ITP a special scoring system with six variables called the Nordic scoringwas done and subsequently followed up at 3 months and 6 months to look for duration of symptoms.
While children with Chronic ITP with secondary causes identified on follow up were excluded in the final analysis.
The proforma are transcribed into Microsoft Excel sheet on Windows 10 software. TheDetails analysedas per statistical description and results were generated.

RESULTS

Total number of children recruited with a clinical diagnosis of primary itp was 120 after excluding the ones which had a secondary cause identified, the total primary itp studied were 100. among them based on the duration of symptoms (as per definitions) they were categorized into newly diagnosed, persistent and chronic ITP.

Table 1: Number of children in newly diagnosed, persistent and chronic ITP recruitedin the study

Sl No	Type	Number
1	Newly diagnosed (acute)	32
2	Persistent	12
3	Chronic	51
4	Secondary causes	8

Age Distribution in Newly Diagnosed ITP:
Age wise Presentation of newly diagnosed ITP –

Table 2: Age wise presentation in newly diagnosed ITP

Sl No	Age	Number	Percentage
1	1-5	16	50%
2	6-10	9	28.125 %
3	>10	7	21.875 %

Age Wise Distribution in Persistent ITP:
The Children with Persistent ITP had following features:

Table 3: Age wise presentation in persistent ITP

Sl No	Age	Number	Percentage
1	1-5	3	25
2	6-10	8	66.66
3	>10	1	8.33

Age Wise Presentation (During the Study Period) –

Table 4: Age wise presentation (during study period) of chronic ITP

Sl No	Age	Number	Percentage
1	1-5	12	23.52
2	6-10	22	43.13
3	>10	15	29.41

Age at Their First Presentation Among Chronic ITP –

Table 5: Age of first presentation of symptoms in chronic ITP children

Sl No	Age	Number	Percentage
1	<1	5	9.08
2	1-5	15	29.41
3	6-10	17	33.33
4	>10	12	23.52

The Severity at Presentation Among Various Types of ITP

Table 6: Severity of presentation in newly diagnosed, persistent and chronic ITP

	Newly diagnosed(%)	Persistent(%)	Chronic (%)
Mild	56.5	68.4	46.7
Moderate	31.6	22.7	44.2
Severe	11.9	8.9	9.1

The Incidence of Preceding Infections (<1m) Among Acute and Persistent ITP Was –

Table 7: Incidence of preceding infections (4weeks prior to onset of symptoms) in newlydiagnosed and persistent ITP children

Preceding infection	Newly diagnosed itp	Persistent itp
Yes	20	7
No	12	5

The Various Haematological Parameters at Presentation:

Table 8: Haematological parameters at presentation in newly diagnosed, persistent andchronic ITP

	Acute ITP (N=42)	**Persistent ITP (N=12)**	**Chronic ITP (N=61)**	**P value**
Hb (g/dl)˚	10.2 ± 2.1	10.4 ± 1.4	11.21 ± 1.21	0.0546
Total count˚	11843 ± 245	11552 ± 350	10833± 523	0.1022
Mean Platelet count˚	14704 ± 1551	17421 ± 1738	16625± 2442	0.0631

The Platelet Count and Severity of Bleeding In newly Diagnosed ITP

Table 9: Platelet count and severity of bleeding in newly diagnosed ITP

Severity	**Platelets <20000/dl**	**Platelets >20000/dl**
Mild	65.8 %	34.2 %
Moderate	72.9 %	28.1 %
Severe	39 %	61 %

There was no statistical correlation or significance (p= 0.3282)

The Platelet Count and Severity of Bleeding In persistent ITP –

Table 10: Platelet count and severity of bleeding in persistent ITP

Severity	**Platelets <20000**	**Platelets >20000**
Mild	66.5 %	33.5%
Moderate	65.2%	34.8%
Severe	100%	0

There is no statistically significant difference. (p- 1.000)

The Platelet Count and Severity of Bleeding In chronic ITP –

Table 11: Platelet count and severity of bleeding in chronic ITP

Severity	**Platelets <20000**	**Platelets >20000**
Mild	30.1 %	69.9 %
Moderate	52.7 %	46.3 %
Severe	71.4%	31 %

There is no statistically significant difference. (p- 0.0842)

Nordic score: the predictive Nordic score assessed for 46 of the newly diagnosed ITP children showed the following results:

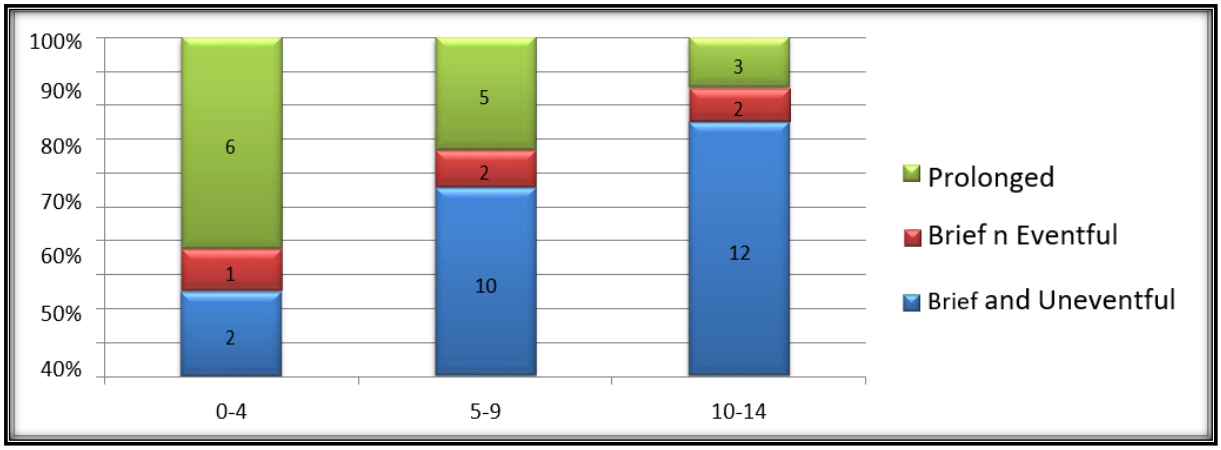

Figure 1: NORDIC SCORING IN NEWLY DIAGNOSED ITP: a comparison of proportion of childrenwith scores of 0-4, 5-9, 10-14 versus their duration of symptomatology

There is a statistically significant difference in the outcomes of those children with scores 0-4versus a score of 10-14. (p- 0.0163).

DISCUSSION

Incidence and Type of ITP –

ITP is a common problem among paediatric population. The incidence of ITP is quoted at 4-5.3 per 100000 children unlike in adults where the incidence is 1.6-2.6 per 100000.[9]

ITP usually presents as an acute onset illness with minor or major bleeds. It usually resolves by 6-12 weeks in most and tends to normalize by 6 months in about 85% of children. However in about 25% children it continues as symptomatic disease. The recent consensus definition accepts this as a time frame cut off to define acute, persistent and chronic disease. About 37% to 50% of chronic ITP remain symptomatic for about 4 years.[10] Similar reports of the proportion of chronic disease in children ranged between 10% and 57%.

This results in increased proportion of ITP patients presenting to a tertiary care centre in a given time frame. In our study time frame we had a total of 100 primary ITP, out of which, 32% were acute ITP, 9% remained persistent in the time frame of the study and the remaining 51% were chronic ITP presenting to our hospital. The disparity in terms of increased proportion of chronic ITP in our study period is attributed to our centre being a tertiary referral for chronic ITP children while most of the acute ITP's get managed at the primary and secondary health care level.

Age of Presentation

ITP typically presents among children between 1 to 10 years of age group, with a peak incidence between 1-3 years of age 25 percentage, 6- 10 age was 21.4 percentage, below 10 years 19.04 percentage. While in our study we had 51 % acute ITP presenting in 6 -10 age group in persistent ITP, 25 percentage in the 1- 5 age group, 66.6 per cent in 6-10 age group, 29.41 per cent in below 10 years.

[Table 5] Age of first presentation of symptoms in chronic ITP children shown 9.08 percentage below 1 year, 29.41 percentage between 1 to 5 year, 39.13 percentage in below 10 years. In a study of 2021 children who had acute ITP, the mean age at presentation was 5.7 years,[11] similar to our study.Although acute ITP may be diagnosed in children of any age, adolescents are more likely to have cITP. In our subset of children with cITP the mean age at presentation was 8 years.

Sex Distribution

There is no sex predilection among children with ITP, even though among infants there are more boysthan girls presenting with ITP.[12] In some cohorts, there is a slight predilection to boys across age groups among acute ITP. Kalim et al in 2005 reported similar distribution among children with acute ITP. The ratio decreases with increasing age. In our study we had more boys than girls among acute and persistent ITP, and more girls among chronic ITP.

Hence, although in children ITP is seen equally in males and females, in adults, ITP is seen predominantly in females by a 1.2:1 ratio. In our cohort of children with cITP, slight female preponderance was observed in consistent with a study done by AH Shaban et al. in Iraq.[13]This may emphasize the fact that female gender has higher chance of chronicity.

Sites of Clinical Bleeding at Presentation

The commonest bleeds among all types of ITP reported from various studies are skin bleeds. In our study it was found over 90% of acute, persistent and chronic ITP had skin bleeds.

While in a study that discussed about the presentation of 60 children presenting with chronicITP, 70% of them have had skin bleeds.[13]

With regards to various sites of bleeding manifestations other than skin bleeds, in our study the acute ITP presentation included 20% Epistaxis, and 20% gingival bleeding, and 4% with hematuria and 5% menorrhagia ,4% with malena, and 1.5% IC bleed. While among the persistent ITP children 92% had skin bleeds, 23% had Epistaxis, 23% had gum bleeds, 7.6% with menorrhagia and none with malena, hematuria, Intra cranial or subconjunctival bleed. In Chronic ITP presentation it included 91% with skin bleeds, 30% with gingival bleeding, 11% with Epistaxis, 7.6% hematuria, 2.5 % each of malena and menorrhagia. 3.7% IC bleed and 2.5% sub conjunctival bleeds. A similar observation was made by Qiu- Xia Fan et al in their study where skin bleeds was 84 and 88%,[14] epistaxis 24 and 23%, gingival bleeding in 34% and 5%, malena in 6.5 and 6% of acute and chronic ITP respectively.

Severity of Bleeding –

Severe bleeding is that involving severe episodes which warrant hospitalization with or without transfusions.[3] Neunert in 2008 published data on 1100 children with ITP. Out of the 863 evaluable children, 77% have had mild clinical bleeds, 20% have had moderate and the rest 3% have had severe bleeds. In our study the overall children with mild bleeding were 58% (57%, 69%, 48% in acute, persistent and chronic ITP respectively), moderate bleeding were 33% (33%, 23%, 43% acute, persistent and chronic ITP) and a higher percent of children presenting with severe bleeds with overall incidence of 8.6% with the distribution of 9.3% of acute, 7.7% of persistent and 8.9% of chronic presenting with severe form of bleeding. This higher proportion of severe bleeding among children as compared to literature could have been because of the tertiary referral nature of our set up.[15]

Overall, the quality of reporting of bleeding in ITP was low in the majority of ITP studies because theyreported bleeding by its presence or absence only, by its anatomical site only, or without clear definitions of severity grades.

ICH IN ITP

Intracranial bleeding is considered a major complication of ITP. There are various estimates of the incidence of ICH in ITP. The fear if ICH is the commonest reason for admission among the children with ITP, the majority of ICH events do not occur during the first few days after diagnosis but later in the course of the disease.[16] The risk of ICH was 0.9% in

another series of 1693 children in a comparative prospective study including 2540 newly diagnosed children with ITP. In our cohort we had 3 children with proven ICH. The incidence is at 1.8% and 3.7% of acute and chronic ITP. This figure, however, is an overestimation, reflecting thatas we are a tertiary care centre therefore it's likely that the most severe cases present here. Whatever the true incidence of ICH in children who have acute ITP, there is no doubt that this event is a fatal complication in this benign childhood disorder. Similarly, Arya et al. from India reported intracranial haemorrhage in 8 cases (3.3%); 6 of these children had chronic ITP at the time of presentation with intracranial haemorrhage.[17]

Preceeding Infection

There is a prior history of infection present in about 60% of paediatric cases of ITP (18). Naureen Mushtaq, in his 10 years experience in a tertiary care hospital also looked into the common precipitating infections which included Acute Gastroenteritis in 14.7%, Upper Respiratory Tract Infections in17.9%, Fever in 24.2%, and Chicken Pox in 3.2% accounting for the overall 35% ITP with preceeding illnesses. While in our study the overall estimate was 66.66 % newly diagnosed ITP and 16.66 % of persistent ITP had a preceeding illness. However, a similar data in the chronic ITP cohort could not be established due to recall bias. In conclusion, further attention to ITP-specific bleeding measurement in clinical trials is needed to improve standardization of this important outcome for patients.

CHRONIC ITP:

About 10–20% of children will fail to remit over six months (chronic ITP). However, we have had 9.1% of the total ITP children in the chronic category while 46.7 and 44.2 were mild, moderate categeory. And as stated before this is more likely in older children, especially adolescent girls. Underlying diseases may be present (for example, systemic lupus erythematosus) and should be sought.

About 7 of the chronic ITP's when followed up during the study period were excluded from the study as they turned out to be SLE. While the rest of them on Long term follow up of children with chronic ITP have shown that remissions continue to occur over a prolonged period. One similar study shows that remissions continue even 10 years after diagnosis with apredicted spontaneous remission rate 61% after 15 years and 63% remission in another series.[19] Many individuals who do not remit, nevertheless run a chronic course with moderate rather than severe thrombocytopenia (by platelet count) and no significant symptoms. Similar findings were seen in Bolton-magg's ITP study.[20]

Role of Bone Marrow Investigation in ITP:

There is a consensus that bone marrow aspiration is not necessary for children who have newly diagnosed typical ITP. The result of the retrospective study of bone marrow aspirates performed in children who have suspected acute ITP showed no signs of leukaemia in case of typical lab feature of ITP. A similar observation was made in our study. Hence, a bone marrow examination therefore shouldnot be considered mandatory in typical cases of childhood acuteITP, unless with atypical features defined as those who have prolonged fever, bone pains and unexplained anaemia, neutropenia or macrocytosis,lymphadenopathy, hepatospleenomegaly. Certainly, the diagnosis should be questioned, particularly in those children who fail to respond and will therefore need a bone marrow for evaluation of the diagnosis. Similar consensus was drawn in another study.[21]

However, based on the ITP review article on future advances it has been argued that In resource-poor countries like India, the accuracy of automated cell counters is not uniformly reliable and hence a low threshold is required for assessing the marrow.[22]

NORDIC SCORE:

As mentioned earlier a scoring system named NORDIC SCORE was designed by Edslev et al,[8] in 2007 after his study in a cohort of ITP children from the Nordic countries. The same scoring with six simple variables used to predict the duration of symptoms was subsequently applied by Yakobovich et al in 2013 in a cohort of newly diagnosed ITP children in Isreal and found out that age <10 years and acute onset with duration of symptoms<2weeks were the best predictors of shorter duration of symptoms.

Subsequently, in a study published in 2013, author Shoushana Revel-Vilik noted that a high Nordic score of 10-14 associated with 71% rapid recovery and 21% rapid recovery with low score.[23] Similar to the above mentioned studies, our cohort of newly diagnosed ITP when scored at admission and subsequently followed up, also showed 75% of rapid recovery with high Nordic scores and 25% with low Nordic scores. This difference in the proportion of outcomesbetween high and low Nordic scores was statistically significant among children with acute ITP.

Strengths of the study:

- Since the study was done in a tertiary care referral centre the incidence of the study was higher than most population based cohorts.
- The total number of children included met the large sample size intended to study the severity of clinical bleeding.
- The number of children were equally distributed between acute and chronic making the study of characteristics unique to this cohort.
- This is the first study from this country which studied about the relevance ofNORDIC score in predicting the duration of symptoms in acute ITP.

Limitations of the study:

- It was a prospective cross sectional study where the response to treatment oroutcomes could not be analyzed.
- NORDIC score could not be matched to their outcomes in about 9% of acute ITP due to loss to follow up.
- It is a single centre study making the presentations and outcomes are not valid to general population.

CONCLUSION

In conclusion, ITP is a common cause of thrombocytopenia in children. Children between the ages of 1 and 10 years old are most typically affected, with an equal number of boys and girls affected. Clinical profiles of acute and chronic ITP in our study were comparable to those found in previous Indian and international investigations. Children with serious bleeds were found to be overrepresented in our sample, which may be due to the fact that the research centre is an outpatient referral tertiary care facility. Among patients with acute and persistent ITP, there was no statistically significant relationship between platelet count and severity of bleeding. However, in chronic ITP with lower platelet counts, there was a trend toward greater severe bleeds.To determine the duration of symptoms associated with acute ITP, the Nordic score may be beneficial; however, larger sample size is required to reach this conclusion.

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