



CLINICAL PROFILE OF CHILDREN WITH PRIMARY IMMUNE THROMBOCYTOPENIA AND FACTORS PREDICTING POOR RESPONSE TO INITIAL TREATMENT.

Paediatrics

Shravan Kanapartha Senior resident, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India. - Correspondence Author

Prashant B Naik Associate Professor, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India

Pushpa G Kini Professor, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India

Shrikiran Aroor Professor and HOD, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India.

Nalini Bhaskaranand Professor, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India

Kalyan Chakravarthy Konda Senior resident, Department of Paediatrics, Kasturba Medical college, Manipal, Manipal University, India.

ABSTRACT

Childhood immune thrombocytopenia (ITP) is an autoimmune bleeding disorder. Most children recover with initial treatment, but the individual course is hard to predict. The objectives were to study the clinical profile of children with Primary ITP and to identify factors that may predict poor response to initial treatment.

Methods: It is a retrospective & prospective study done in a tertiary hospital. 29 Acute ITP & 26 Persisting/Chronic ITP cases are studied.

Results: Acute ITP group was characterized by younger age of onset ($p=0.003$), duration of symptoms at presentation <2 weeks ($p <0.001$) and relatively high absolute lymphocyte count ($p=0.019$). Children in chronic ITP group had presented at older ages with low absolute lymphocyte count. However, the difference was statistically insignificant.

KEYWORDS:

Immune thrombocytopenia; Idiopathic thrombocytopenic purpura; ITP; Platelet disorders; lymphocyte number.

MAIN TEXT

Abbreviations: ITP-Immune thrombocytopenia, IVIg: Intravenous Immunoglobulin, IgA: Immunoglobulin A, IgG: Immunoglobulin M, IgM: Immunoglobulin G.

INTRODUCTION

Immune thrombocytopenic purpura (ITP), previously known as Idiopathic Thrombocytopenic purpura, is an immune-mediated acquired disease characterized by a transient or persistent decrease of the platelet count. Two-thirds of children with acute ITP recover within six months but, in some, the disease may persist for longer periods. Identification of the prognostic factors would help in predicting the course of disease and in alleviating the parental anxiety. AIMS AND OBJECTIVES: To study the clinical and laboratory profile of children with Primary ITP and factors that may predict poor response to initial treatment.

MATERIALS AND METHODS

It is a retrospective & prospective observational study conducted in a tertiary hospital over 56 months. Cases were followed up for a minimum period of 3 months from diagnosis.

Inclusion criteria:

Children between 1 month to 18 years of age with clinical features suggestive of ITP and platelet count $< 1,00,000/$ cumm (in the absence of any other cause) with a follow-up for a minimum of 3 months after initial treatment were included in the study.

Exclusion Criteria: Children with thrombocytopenia due to other Auto-immune diseases (e.g. SLE), on Chemotherapy and who received treatment outside before presenting to Kasturba Hospital were excluded.

Definitions [1].

- **Primary ITP:** Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count $<1,00,000/$ cumm) in the absence of other causes or disorders that may be associated with thrombocytopenia
- **Newly diagnosed/Acute ITP:** Children with thrombocytopenia with platelet count less than 1, 00,000/cumm for less than three months.
- **Persistent ITP:** ITP lasting between 3 and 12 months from diagnosis.
- **Chronic ITP:** Children with ITP in whom thrombocytopenia persists for more than 12 months.

Prior approval of Institutional ethics committee was obtained. Relevant clinical history was collected from the parents/guardians for prospective cases, and medical records were utilized for retrospective cases. Complete blood picture with peripheral smear at admission was done in all cases. Immunoglobulin levels at admission were analyzed only in prospective cases.

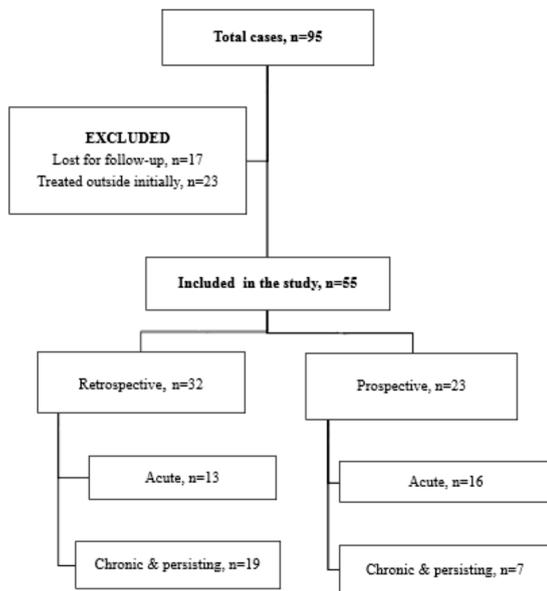
Data was analyzed using IBM SPSS (Statistical Package for Social Sciences) statistics 20 software. Numerical data were presented as a median and interquartile range. Independent sample t-test (Mann-Whitney test) and Chi-square test with Fisher's exact were used for data analysis of continuous and categorical variables respectively. A p -value < 0.05 was considered significant.

RESULTS

Figure 1 depicting the flow diagram of the study group. A total of 95 cases with primary ITP attended the Department of Paediatrics during the study duration, out of whom 23 received treatment outside initially and 17 were lost to follow-up, and hence were excluded. 55 cases were

included, 29 with Acute ITP and 26 with chronic/persisting ITP. Out of the 55 cases, 32 were analyzed retrospectively, and 23 were analyzed prospectively.

Figure 1, Flow diagram of study cohort.



Baseline parameters of the study group are shown in Table.1. In the present study female: male ratio was 1.2. Acute ITP was more commonly seen in younger children whereas chronic ITP was more common in older children with a statistically significant p-value.

Table.1, Summary of baseline parameters in children with ITP.

	Acute ITP (n=29) %	Chronic & Persisting ITP (n=26) %	p value
Sex			
Male (n=25)	15(51.7%)	10(38.5%)	0.324 (NS)
Female(n=30)	14(48.3%)	16 (61.5%)	
Age (y.)			
1month-3	13	2	0.003 (S)
3-6	6	6	
6-9	5	6	
9-12	4	2	
12-15	1	9	
15-18	0	1	
Seasonal variation			
Dec-March	11	14	0.035 (S)
April-July	7	9	
Aug-Nov	11	2	
Symptomatology*			
Skin bleed	26	19	
ENT & mucosal bleed	11	10	
CNS bleed	1	0	
Menorrhagia	1	4	
Duration of onset of symptoms at diagnosis			
<2weeks	26	10	<0.001 (S)
>2 weeks	2	15	
Asymptomatic	1	1	
H/o fever (within 4 weeks of onset of symptoms).			
Yes	11	8	0.577(NS)
No	18	18	
Platelet count/ cumm. (median/IQ 75th,25th)	5000 (11000, 4000)	10000 (23500,4000)	0.18 (NS)
Total leucocyte count/ cumm. (median/IQ 75th,25th)	12300 (16100,8500)	9200 (12925,7950)	0.085 (NS)

Absolute lymphocyte count/ cumm (median/IQ 75th,25th)	4291 (7142,3059)	2992.5 (4409.5,2184)	0.019 (S)
Immunoglobulin (mg/dl) (median/IQ 75th,25th)			
IgA	65.5 (95,48.25)	76 (143, 49.5)	0.643 (NS)
IgM	123.5 (140,72)	91 (128, 71.5)	0.517 (NS)
IgG	1011.5 (1277.5,853.5)	944 (1149.5, 838)	0.459 (NS)
Initial treatment received.			
Steroids	18 (62%)	18 (69.2%)	
IVIg	10 (34.48%)	5 (19.2%)	
Observation	1 (3.44%)	3 (11.5%)	

*Overlap of symptoms is present

Chronic/persisting ITP was most commonly seen between December-July, and acute ITP cases were common during August-November. However, the difference was not statistically significant. Skin bleed followed by mucosal bleed were the most common presenting symptoms. The life-threatening bleed was rare and was seen in only one child. Most of the acute ITP cases (26/29) presented within two weeks of symptom onset. On the contrary, chronic ITP cases presented late, i.e., >2weeks after the onset of symptoms (p-value:<0.001). There was no significant difference in preceding fever in acute (11/29) and chronic groups (8/12). Median platelet count at presentation was 5000/cumm and 10000/cumm in acute and chronic groups respectively (p-value:0.18). Total leucocyte count at admission was high in acute(12300/cumm) when compared to chronic ITP group (9200/cumm) with a p-value of 0.085. Children with Acute ITP had a relatively higher absolute lymphocyte count when compared to Chronic ITP group (4291 vs. 2992.5 with a p-value of 0.019). There was no significant difference in Immunoglobulin levels between the two groups. Most of the children received steroids as the initial treatment.

Discussion:

Immune thrombocytopenia, with a backdrop of autoimmunity as pathogenesis, was more common in females in chronic/persisting ITP group (p=0.324) and was in line with other studies [2,3]. Similarly, the chance of progressing to a chronic disease was higher in older age group children. Younger age of onset predicted a favorable response to initial treatment (p-value:0.003), with similar results in other studies [3-6,9].

The seasonal variation observed between the two groups could be explained by the fact that most of the children in monsoon would have had a preceding viral illness followed by immune thrombocytopenia, which most of the times shows a good response to the initial treatment. Zeller et al. [6] reported similar results, but Bolton et al. [7] found no seasonal variation.

Skin bleeding manifestations followed by mucosal bleeds were the most common manifestations. Severe bleeding manifestations are rare in children with ITP in spite of very low platelet counts. One child in the study group had intracranial bleed and manifested as seizures. In Glanz et al., mucosal bleeds were more commonly associated with chronic ITP [4].

Insidious onset of symptoms (>2weeks) was associated with chronicity with a significant p-value (p<0.001) and was in line with other studies [2,6,8].

No significant difference between median platelet counts and total leucocyte count was observed in the present study. Higher platelet counts (>20000/cumm) at presentation were found to be a predictor of chronicity in other studies [2,4]. Higher absolute lymphocyte count (p=0.019) with an Area Under Curve of 0.684± 0.073 at presentation is observed in children with acute ITP group. Similar results were observed in other studies [2-4,9].

In the present study, immunoglobulin levels were estimated in the prospectively studied cases at initial presentation which did not receive any form of treatment outside to remove the possible bias. Median IgM & IgG levels were higher and median IgA levels lower in children with acute ITP compared to chronic ITP, however, the difference was not statistically significant. In a study by Masaru et al., elevated levels of

IgA, IgG, and IgM were seen in children with acute ITP [11]. A study by Arnason et al. showed elevated IgA and low IgM levels was associated with a significantly increased chance of failing to respond to initial treatment [11].

Steroids were the predominant 1st line medication used followed by IVIg in both groups. One child with chronic ITP in the study group expired. He presented with altered sensorium and mucosal bleed. Poor drug compliance was reported.

Conclusion

Identifying factors that help in assessing the prognosis of children with Immune Thrombocytopenia would assist clinicians in educating parents about the specific information and likely course of the disease and helps in alleviating their anxiety. Younger age at onset, acute onset of symptoms (<2 weeks), presentation during August-November, higher absolute lymphocyte count at presentation were associated with good prognosis.

Limitations: A well-structured prospective randomized trial with a larger sample size would facilitate identification of risk factors and assess the efficacy of various available medications.

No conflict of interest. No source of funding.

Acknowledgement: None

REFERENCES:

- 1) Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an International Working Group. *Blood*. 2009;113:2386-93.
- 2) Katja M. J. Heitink-Poll, Joyce Nijsten, Chantal W. B. Boonacker, Masja de Haas, Marrie C.A Bruin. Clinical and laboratory predictors of chronic immune thrombocytopenia in children: a systematic review and meta-analysis. *Blood*. 2014;124(22):3295-3307.
- 3) Lowe EJ & Buchanan GR. Idiopathic thrombocytopenic purpura diagnosed during the second decade of life. *Journal of Pediatrics*. 2002; 141, 253–258.
- 4) Glanz J, France E, Xu S, Taru Hayes, Simon Hambidge. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Pediatrics*. 2008;121, e506–e512.
- 5) Kuhne, T, Buchanan G.R., Zimmerman S, Lisa A, Regina K, Willi Berchtold et al. For the Intercontinental Childhood ITP Study Group. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the Intercontinental Childhood ITP Study Group. *Journal of Pediatrics*. 2003;143, 605–608.
- 6) Zeller B, Rajantie J, Hedlund-Treutiger, Tedgard U, Wesenberg F, Jonsson OG, et al. Childhood idiopathic thrombocytopenic purpura in the Nordic countries: epidemiology and predictors of chronic disease. *Acta Paediatrica*. 2005;94, 178–184.
- 7) Bolton-Maggs PHB & Moon I. Assessment of UK practice for management of acute childhood idiopathic thrombocytopenic purpura against published guidelines. *Lancet*. 1997;350, 620–623.
- 8) L G Robb, K Tiedeman, Idiopathic thrombocytopenic purpura: predictors of chronic disease. *Archives of Disease in Childhood*. 1990;65: 502-506
- 9) Ahmed I, Rajpurkar M, Thomas R, Chitlur M. Initial lymphocyte count and the development of persistent/chronic immune thrombocytopenic purpura. *Pediatric Blood & Cancer*. 2010;55(3): 508-511.
- 10) Masaru Kubota, Ikuya Usami, Kenichiro Kobayashi, Tsutomu Tsutsui, Kousaka Matsubara. Serum Immunoglobulin Levels at Onset: Association with the Prognosis of Childhood Idiopathic Thrombocytopenic Purpura, *International Journal of Hematology*. 2003;77:304-307.
- 11) Jon E. Arnason, Federico Campigotto, Donna Neuberg, James B. Abnormalities in IgA and IgM are associated with treatment-resistant ITP. *Blood*. 2012;119(21): 5016-5020