



Research Article

Clinical profile and outcome of newly diagnosed Immune Thrombocytopenia in Children

Authors

Thekkile Gangadharan Sindhu¹, Lakshmi Raj², Mohandas Nair Karipppoth^{3*}, Kinattinkara Ramachandran Subbaraman⁴

¹Associate Professor, Department of Pediatrics, Government Medical College Kozhikode, Kerala

²Senior Resident, Government Medical College Thiruvananthapuram, Kerala

³Additional Professor Department of Pediatrics, Government Medical College Kozhikode, Kerala

⁴Professor Department of Pediatrics, Malabar Medical College, Modakalloor, Atholi, Kozhikode, Kerala

*Corresponding Author

Mohandas Nair Karipppoth

Additional Professor Department of Pediatrics, Government Medical College Kozhikode, Kozhikode, Kerala, India 673008

Phone No: 9447191560, Email: mohandas_nair68@yahoo.com

Abstract

Introduction: Immune thrombocytopenia (ITP) is a common cause of bleeding and often a cause of concern in children. This study was conducted to describe the clinical profile of children with newly diagnosed ITP and to identify the risk factors for development of persistent ITP.

Materials and Methods: Hospital based descriptive longitudinal study conducted from January 2015 to June 2016 among children 12yrs and below admitted with a clinical diagnosis of newly diagnosed ITP. Details of history, clinical examination, investigations and treatment were noted. They were followed up for 6 months to monitor for development of Persistent ITP. Data was analyzed using SPSS software.

Results: Among the 90 children 22 (24%) turned out to be persistent ITP. Most of the children were < 5 years old. The male female ratio was 1:1.2. Majority of children had grade 1 bleed. All the children had cutaneous bleeds; other bleeding manifestations were oral mucosal bleed, epistaxis, gastrointestinal bleed, subconjunctival hemorrhage and hematuria. Profound thrombocytopenia was found in about one third of cases. Bone marrow examination findings were consistent with ITP. Majority of the children were conservatively managed. None of them developed major complications like intracranial bleed. The risk factors for development of persistent ITP were identified as splenomegaly, profound thrombocytopenia and grade 2 bleed.

Conclusions: Most of the children in this study were < 5 years old. 24% of children turned to be persistent ITP. Bone marrow examination findings were normal. The risk factors for development of persistent ITP were identified as splenomegaly, profound thrombocytopenia and grade 2 bleed.

Keywords: Immune thrombocytopenia, Persistent ITP, Clinical predictors.

Introduction

Immune thrombocytopenia (ITP) is not an uncommon problem encountered in childhood population. The disease usually is acute, self-limited, and follows a benign course in most children^[1]. Approximately 20% of ITP cases progress to chronic form. There has been an International Working Group (IWG) consensus panel consisting of experts in ITP which recently provided guidance on terminology, definitions, and outcome criteria for this disorder. ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (>12 months' duration)^[2]. A presumptive diagnosis of ITP is made when the history, physical examination, complete blood count, and examination of the peripheral blood smear do not suggest other etiologies. There is no "gold standard" test that reliably establishes the diagnosis of ITP. Bone marrow evaluation is recommended only when abnormalities are present in the blood count/smear, or if systemic features like bone pain are apparent, has an otherwise unexplained enlarged spleen.^[3] Bone marrow evaluation should be considered in cases who respond minimally or not at all to first-line therapies. The major goal for treatment of ITP is to provide a safe platelet count (one that prevents major bleeding) rather than correcting the platelet count to normal levels. The management options depend on the clinical severity and includes expectant watch and wait policy, IVIG, steroids and Anti-D. There is lack of consensus regarding management of the disease. The major complication that is anticipated is intracranial bleed (incidence is very less)^[4]. and this may lead to treatment in unnecessary cases. One of the treatment modalities being used in ITP is steroids which is a cheaper alternative to IVIG. Even though literature describes that bone marrow is not indicated in a typical presentation of ITP^[3,5,6]. in our setting, steroids are usually started only after bone marrow evaluation— to rule out secondary causes of ITP such as malignancies. This study attempts to assess the clinical profile of

newly diagnosed ITP cases and to study the occurrence, if any, of major complications. It also attempts to identify the indications and findings of bone marrow evaluation and the risk factors for developing persistent ITP.

Materials and Methods

This hospital based descriptive follow-up study was conducted at a major tertiary care teaching hospital under government sector in North Kerala. All newly diagnosed ITP cases admitted during January 2015 to June 2016 were included. Children presented after receiving specific treatment from outside and neonates were excluded from the study.

Detailed history including preceding viral infection, recent immunization in the preceding three months and family history of any bleeding conditions were noted. All types of bleeding manifestations looked and were graded as per the IWG consensus guidelines into grade 1 to 4. During clinical examination emphasis was given to pallor, lymphadenopathy, hepatosplenomegaly, bone tenderness. Investigations like Complete blood count, peripheral smear, ESR, bleeding time, PT, APTT were done for all patients. Bone marrow evaluation was done in all clinically indicated cases and before starting steroid treatment. Direct Coombs Test (DCT) was done in all cases with anemia. Special investigations like ANA IF and HIV testing were done in all persistent cases and in children with atypical features. Treatment details were noted. A platelet counts less than $100 \times 10^9/L$ was established as the threshold for diagnosing ITP. Anemia (defined as hemoglobin less than 11gm% in children ≤ 6 years and less than 11.5gm% in children >6 years). The children were followed up at 1 month, 2-month, 3 months, 6 months and more often if clinically indicated. During each follow up visit clinical examination for any bleeding and testing platelet count were done. The details of treatment during follow up were noted. Response was defined as per IWG consensus guidelines. Any child having persistent thrombocytopenia 3

months after onset were classified as persistent ITP. Data was analyzed using SPSS software and the risk factors for persistent ITP were estimated using crosstabs.

Written informed consent was obtained from all cases. Ethical clearance was obtained from the institutional ethics committee. (GMCKKD/RP2015/IEC/07/01 dated 5/1/2015)

Results

A total of 90 children were included in the study; All of them were followed up for a minimum period of 6 months. Age of the patients ranged from 8 months to 12 years and the mean age at diagnosis was 4.63 years (Table 1). Of the 90 children included in the study, there were 49 girls and 41 boys. The female to male ratio was 1.2:1. History of recent infection were present in 11 (12.2%) children. None of them had any recent vaccination. There was no significant family history.

On clinical examination 6 (6.6%) children had splenomegaly, 5(5.5%) children had significant lymphadenopathy and 3 (3.3%) had hepatomegaly. All the children had cutaneous bleeds; other bleeding manifestations were oral mucosal bleed, epistaxis, gastrointestinal bleed, subconjunctival hemorrhage and hematuria. (Table 2) Majority had only grade 1 bleeds. (table 3)

28 children had a platelet count less than 10,000 at the time of presentation. (figure 1).

Anemia was present in 28 cases (31.1%). Eight of them had persistent ITP. The mean hemoglobin values ranged from 7 to 14.6gm%. DCT was found to be negative in all these children with anemia.

Peripheral smear examination was done in all children; findings were consistent with ITP. Two children had increased atypical lymphocytes which was followed up with bone marrow examination.

Bone marrow examination was done in 48(53.3%) of the total 90 children. The findings were consistent with ITP in all the cases. 31 children had increased megakaryocytes on bone marrow

examination and 17 had normal number of megakaryocytes. The indications for bone marrow study were to initiate steroids (33:68.9%), Severe thrombocytopenia and wet bleeds anticipating use of steroids (11;22.9%), When readmitted with bleeding manifestations (2) and follow up of suspicious peripheral smear finding (2)

ANA-IF was done in all cases of Persistent ITP and 10 cases of Newly diagnosed ITP; the results were positive in 3 cases (2 were newly diagnosed ITP and the other was persistent ITP).

During the initial presentation, 59 (65.5%) children were treated conservatively, 12(13.3%) children required IVIG alone, 15 (16.6%) children required steroids alone, 3 children were given IVIG and steroids and 1 child was given IVIG, steroid and Anti-D. Of the children who developed persistent ITP and who required steroids on subsequent admissions, the initial management given was – conservative treatment in 6 cases, IVIG in 4 cases, steroids in 2 cases, IVIG with steroids in 2 cases; 1 child who was conservatively managed initially was given steroid with Anti-D on subsequent admission.

Average time for response with IVIG was 1.6 days and with steroids was 5.6 days.

All of them were followed up for 6 months. 22 (24.4%) children were turned out to be persistent ITP on follow up. Half of them were less than 5 years of age. But this was not statistically significant. (p value - 0.886) The male female ratio of this group was 1:1

None of the children had significant lymphadenopathy or hepatomegaly; But 4 had splenomegaly. This was significantly high compared to those who did not turn out to be persistent ITP. (p=0.013) The children with newly diagnosed ITP who had splenomegaly has 7.3 times risk to develop persistent ITP (Relative risk – 7.33).

Among the children who turned out to be persistent ITP, 3 children (13.6%) presented with grade 1 bleed, 11(50%) with grade 2 bleed and 8(36.3%) with grade 3 bleed. None of these children had

grade 4 bleed. 7.1% of children with grade 1 bleed, 52.4% children with grade 2 bleed and 29.6% with grade 3 bleed turned to be persistent ITP. Half of the persistent ITP cases were found in children with grade 2 bleed, the association was found to be statistically significant (P value < 0.001).

Most of the children (46.4%) with persistent ITP was found in the platelet count range of <10000. The relationship was found to be statistically significant (p value – 0.003).

Anemia (defined as hemoglobin less than 11 gm% in children \leq 6 years and less than 11.5 gm% in children >6years) was present in 8 cases of persistent ITP. DCT was negative in all the 8 children. 28.6% of children with anemia developed persistent ITP; The relationship was found not to be statistically significant (p value – 0.540). Bone marrow examination was done in 19 cases of persistent ITP and all had findings consistent with ITP. HIV screening was done in all children with persistent ITP and was negative in all. ANA-IF was done in all cases of persistent ITP and was positive in one child. 33.3% children with ANA-IF positivity developed persistent ITP. The relationship was found not to be statistically significant (P value – 0.716).

Of all the 22 children with persistent ITP, during the initial presentation, 10 children (45.4%) were treated conservatively, 3 children (13.6%) were given IVIG alone, 5 children (22.7%) were given steroids alone, 3 children (13.6%) were given IVIG and steroids and 1 child(4.5%) was treated with IVIG, steroid and Anti-D.

All the children who had received IVIG with steroids as well as IVIG with steroids and Anti-D developed persistent thrombocytopenia. The relationship was found to be statistically significant (p value – 0.005). The number of hospitalization in cases of persistent ITP ranged from 1 to 8. The mean number of hospitalization was 5 days.

At the end of the study period – Of the 22 children who turned to be persistent ITP, 11 were asymptomatic with normal platelet counts; 11 children had thrombocytopenia with bleeding manifestations. One child with persistent ITP is on Danazol; all other children were on oral steroids when severe bleeding manifestations were present.

Table 1 Age distribution

Age group	Number of patients N=90	Percentage %
<5 years	41	45.5%
5 - < 10 years	35	38.8%
\geq 10 years	14	15.5%

Table - 2 Type of bleed

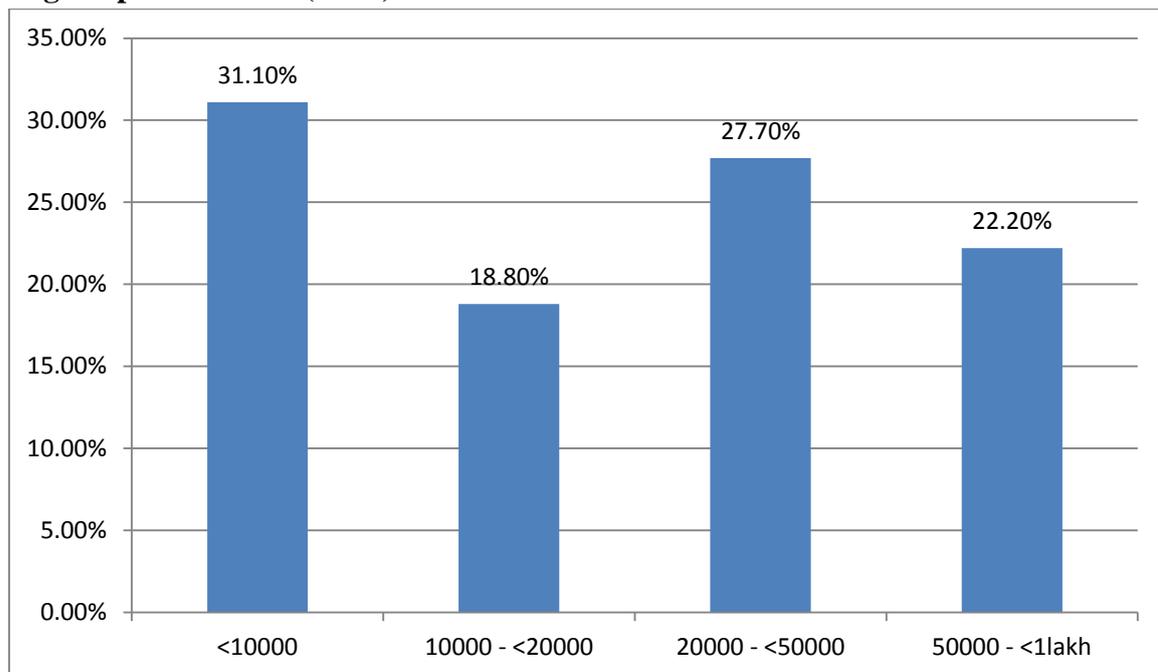
Type of bleed	Number of patients N=90	Percentage %
Cutaneous bleed	90	100%
Oral mucosal bleed	13	14.4%
Epistaxis	7	7.7%
GI bleed	4	4.4%
Subconjunctival hemorrhage	2	2.2%
Hematuria	1	1.1%
*one child can have multiple types of bleed		

Table - 3 Grade of bleed

Grade of bleed	No of patients N=90	Percentage
Grade 1	42	46.6%
	21	23.3%
Grade 3	27	30%
Grade 4	0	0

Table 4 Initial platelet count: Total cases and Persistent ITP (n=90)

Platelet count	Total no of cases N=90	Persistent ITP cases n=22	Percentage
<10000	28	13	46.4%
10000 - <20000	17	5	29.4%
20000 - <50000	25	3	12%
50000 - < 1lakh	20	1	5%

Figure-1 Range of platelet count(n=90)

Discussion

The objective was to study the clinical profile, investigations and treatment in newly diagnosed ITP and to identify the risk factors for persistent ITP.

The mean age at diagnosis was 4.63 years and majority of the children (45.5%) belonged to the age group of <5 years. Our findings were similar to the study by Demircioglu F et al,^[7] in which the mean age of diagnosis was 5 years. In a study conducted in Netherlands by Bruin M et al^[8] the mean age of diagnosis was 7.1 years.

Among the 90 children majority were girls (54.5%) and the female to male ratio was 1.2:1. This was similar to the study by Bruin M et al^[8] where the female to male ratio was 1.2:1. Whereas in the Croatian study conducted by Roganovic J et al,^[9] equal incidence was found in males and females (female to male ratio – 1:1).

Of the 90 children enrolled in our study, 12.2% had history of some infection preceding onset of symptoms. In the study done by Bruin M et al^[8] 60% children had some preceding infection. In the Korean study by Sohn YM et al,^[10] 43.3% of the children had preceding infection and in the intercontinental study by Tamminga R et al^[11] 55% children with ITP had preceding infection.

Most of the children (31.1%) had platelet count less than 10000/cu.mm (profound thrombocytopenia) in our study. The finding in our study was similar to the findings by Roganovic J et al^[9] and Bruin M et al^[8]. were more than 50% and 60% children respectively had platelet count less than 10000/cu.mm. Whereas in a study conducted by Kuhne T et al^[12] majority had platelet count in the range of 10000 -<20000/cu.mm. The admission criteria followed by different institutes may affect this.

Among the total 90 children 22 (24.4%) turned out to have persistent ITP. This data was similar to the observations by Glanz J et al (23%)^[13] and Demircioglu et al (16.1%).^[7] Whereas in a study which was conducted by Imbach P et al^[14] persisting thrombocytopenia was found in 74.4% children.

Majority of the children who turned to be persistent ITP (50%) belonged to the age group of < 5 years. No statistically significant association was found between the age of children and development of persistent ITP. Our findings were similar to the study by Bruin M et al^[8] where no significant association was found between age and developing persisting thrombocytopenia. Whereas in other studies older children were at higher

risk^[15,16]. There was no difference in gender distribution in children who developed persistent ITP; female to male ratio was 1:1. Similar findings were seen in the study conducted by Kubota M et al^[17], where no significant association was present between gender of the child and risk of developing persisting thrombocytopenia. But in the study by Bruin M et al^[8], majority of children who developed persisting thrombocytopenia were girls and were found to have a 3-fold risk (p value-0.07)

4 children with splenomegaly developed persistent ITP and the association was found to be statistically significant (p value -0.013).

Most of the cases of persistent ITP occurred in children with grade 2 bleed and the association was found to be statistically significant. Bruin M et al^[8] observed that no relationship was found to be present between grade of bleed and development of persisting thrombocytopenia.

Majority of the children with persistent ITP were in the platelet count range of less than 10000/cu.mm. The finding has a statistically significant association (P value – 0.003). This was similar to the study by Kubota M et al.^[17] But others have documented turning to be persistent ITP when the initial platelet counts are relatively high^[8,13]

All the children who had received IVIG with steroids and IVIG with steroids and Anti-D during initial presentation developed persistent thrombocytopenia. The finding was found to have a statistically significant association (pvalue – 0.005). This maybe because usually treatment is indicated in severe cases of ITP. In the study conducted by Bruin M et al^[8], persisting thrombocytopenia was found more in children who were conservatively managed. Whereas in the study by Kocak U et al,^[18] no significant association was found between the initial treatment modality and persisting thrombocytopenia.

Conclusions

Newly diagnosed ITP was found to be more prevalent in younger children and among girls; a

small group of children had infection before the onset of bleeds; majority of children had minor bleeds in spite of profound thrombocytopenia. Peripheral smear in all cases were consistent with ITP. Most of the children were conservatively managed. There were no major complications like intracranial bleed. Bone marrow examination was done in 48 children (58.3%) of total cases; all had findings consistent with ITP. It maybe suggested that steroids which is a cheaper treatment modality compared to IVIG can be started without a bone marrow evaluation in typical presentation of ITP. The risk of complications including intracranial bleed in newly diagnosed ITP is very less; hence expectant watch and wait policy while management may be followed in most of the cases. Children with newly diagnosed ITP must be followed up for the development of persistent ITP. The risk factors for development of persistent ITP were identified as splenomegaly, profound thrombocytopenia and grade 2 bleed.

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References

1. Psaila B, Bussel JB. Immune thrombocytopenic purpura. *Hematology/oncology clinics of North America*. 2007 Aug 31;21(4):743-59.
2. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, Bussel JB, Cines DB, Chong BH, Cooper N, Godeau B. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009 Mar 12;113(11):2386-93.
3. ITP Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *British journal of haematology*. 2003;120(1):574-96.
4. Hoffman R, Silberstein LE, Heslop H, Weitz J. *Hematology: basic principles and practice*. Elsevier Health Sciences; 2013.

5. Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux IV S. Nathan and Oski's hematology of infancy and childhood. Elsevier Health Sciences; 2008 Dec 16.
6. Anoop P. Immune thrombocytopenic purpura: Historical perspective, current status, recent advances and future directions. *Indian Pediatrics*. 2012;49(10): 811-818.
7. Demircioğlu F, Saygı M, Yılmaz Ş, Ören H, İrken G. Clinical features, treatment responses, and outcome of children with idiopathic thrombocytopenic purpura. *Pediatric hematology and oncology*. 2009 Jan 1;26(7):526-32.
8. Bruin M, Bierings M, Uiterwaal C, Révész T, Bode L, Wiesman ME, Kuijpers T, Tamminga R, Haas M. Platelet count, previous infection and FCGR2B genotype predict development of chronic disease in newly diagnosed idiopathic thrombocytopenia in childhood: results of a prospective study. *British journal of haematology*. 2004 Dec 1;127(5):561-7.
9. Roganovic J, Letica- Crepulja M. Idiopathic thrombocytopenic purpura: A 15- year natural history study at the Children's Hospital Rijeka, Croatia. *Pediatric blood & cancer*. 2006 Oct 15;47(S5):662-4.
10. Sohn YM, Park CS, Kim KY. Idiopathic thrombocytopenic purpura in children: clinical prognosis and evaluation of treatment. *Yonsei medical journal*. 1986 Mar 1;27(1):67-75.
11. Tamminga R, Berchtold W, Bruin M, Buchanan GR, Kühne T. Possible lower rate of chronic ITP after IVIG for acute childhood ITP an analysis from registry I of the Intercontinental Cooperative ITP Study Group (ICIS). *British journal of haematology*. 2009 Jul 1;146(2):180-4.
12. Kühne T, Berchtold W, Michaels LA, Wu R, Donato H, Espina B, Tamary H, Rodeghiero F, Chitlur M, Rischewski J, Imbach P. Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. *Haematologica*. 2011 Dec 1;96(12):1831-7.
13. Glanz J, France E, Xu S, Hayes T, Hambidge S. A population-based, multisite cohort study of the predictors of chronic idiopathic thrombocytopenic purpura in children. *Pediatrics*. 2008 Mar 1;121(3):e506-12.
14. Imbach P, Kühne T, Müller D, Berchtold W, Zimmerman S, Elalfy M, Buchanan GR. Childhood ITP: 12 months follow- up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). *Pediatric blood & cancer*. 2006 Mar 1;46(3):351-6.
15. Yacobovich J, Revel-Vilk S, Tamary H. Childhood immune thrombocytopenia—who will spontaneously recover?. In *Seminars in hematology* 2013 Jan 31 (Vol. 50, pp. S71-S74). WB Saunders.
16. ElAlfy M, Farid S, Maksoud AA. Predictors of chronic idiopathic thrombocytopenic purpura. *Pediatric blood & cancer*. 2010 Jul 1;54(7):959-62.
17. Kubota M, Adachi S, Usami I, Okada M, Kitoh T, Shiota M, Taniguchi Y, Tanizawa A, Nanbu M, Hamahata K, Fujino H. Characterization of chronic idiopathic thrombocytopenic purpura in Japanese children: a retrospective multi-center study. *International journal of hematology*. 2010 Mar 1;91(2):252-7.
18. Koçak Ü, Aral YZ, Kaya Z, Öztürk G, Gürsel T. Evaluation of clinical characteristics, diagnosis and management in childhood immune thrombocytopenic purpura: a single center's experience. *The Turkish journal of pediatrics*. 2007 Jul 1;49(3):250.