Clinical and Morphological Profile of Immune Thrombocytopenic Purpura in Children - A Five Year Study in a Paediatric Tertiary Health Care Centre of South India

Ashida M. Krishnan[1], Deepthi Raj M.L.[2], Priya V.S.[3], Arya R.S[4]

[1, 2, 3, 4] Department of Pathology, Government Medical College, Thiruvananthapuram, Kerala, India.

ABSTRACT

BACKGROUND

Immune Thrombocytopenic Purpura (ITP) is one of the most commonly encountered disease in paediatric practice. Thorough clinical and morphological study of peripheral blood and bone marrow is required for confirming ITP. Clinicomorphological aspects of paediatric ITP is a less studied topic especially in developing countries like India. The objective was to study the clinical and morphological profile of paediatric cases of ITP.

METHODS

This is a 5-year record based retrospective study conducted in a paediatric tertiary health care centre in Kerala, South India. Data of all paediatric cases diagnosed as ITP including clinical presentation, clinical findings, blood counts, peripheral blood morphology, bone marrow morphology, and treatment response was collected and entered in SPSS software version 16.0 and analysed. For assessing correlation, chi-square test was used.

RESULTS

The age of children ranged from 3 months to 15 years. H/o viral fever was noted in 53 % cases. Cases which had moderate and severe thrombocytopenia were 74 % and 21 % respectively. Isolated thrombocytopenia was the most common peripheral blood picture observed with few cases showing coexisting eosinophilia and anaemia. All cases showed megakaryocyte proliferation in marrow with 9 % cases showing coexisting iron deficiency anaemia. Majority of cases showed rapid response to steroid / IVIG therapy and the response had no correlation with grade of thrombocytopenia (p value < 0.05).

CONCLUSIONS

Paediatric cases of ITP usually present following viral infections or vaccination, with worrisome bleeding episodes, petechiae, ecchymosis or purpura.

KEYWORDS

ITP, Paediatrics, Platelet Count, Thrombocytopenia, Vaccination

Corresponding Author:
Dr. Priya V.S.,
Department of Pathology,
Government Medical College,
Thiruvananthapuram, Kerala, India.
E-mail: priyapath.vs@gmail.com

DOI: 10.18410/jebmh/2020/560

How to Cite This Article:
Krishnan AM, Raj DML, Priya VS, et al. Clinical and morphological profile of immune thrombocytopenic purpura in children- a five year study in a paediatric tertiary health care centre of South India. J Evid Based Med Healthc 2020; 7(46), 2724-2729. DOI: 10.18410/jebmh/2020/560

Submission 21-08-2020,
Peer Review 27-08-2020,
Acceptance 24-09-2020,
Published 16-11-2020.

BACKGROUND

Immune thrombocytopenic purpura is an acquired haematological disorder characterized by bleeding manifestations, affecting both adults and children. Being the most common cause of bleeding in children, immediate medical attention is sought in majority of cases.[1] Immune Thrombocytopenic purpura (ITP) can be defined as an autoimmune disorder characterized by antibody mediated destruction of platelet resulting in low circulating platelets and compensatory megakaryopoiesis in bone marrow. Depending on the duration of illness it is classified into acute and chronic types; and based on underlying aetiology it is classified into primary and secondary types. Thrombocytopenia persisting more than 6 months is required for the diagnosis of chronic disease. Primary ITP occurs in the absence of other autoimmune conditions, while in secondary type there will be underlying autoimmune conditions like SLE (Systemic Lupus Erythematosus), common variable immunodeficiency etc. Thrombocytopenia in peripheral blood can occur either due to suppression of megakaryocytes in bone marrow or increased destruction of platelets in the periphery.[2] Viral infections suppressing megakaryopoiesis, aplastic anaemia, neoplastic bone marrow infiltrates, consumption coagulopathies like HUS (Haemolytic Uremic Syndrome) and splenic sequestration are common conditions which can cause peripheral thrombocytopenia in children and ITP is often a diagnosis of exclusion. A thorough clinical examination followed by biochemical, serological and detailed haematological work up is essential in all cases presenting with bleeding manifestations.[3] Since steroids and Intra Venous Immuno-globulins (IVIG) are the main therapeutic intervention in immune thrombocytopenic purpura, bone marrow examination becomes a very crucial investigation to differentiate destructive thrombocytopenia like ITP from other causes like infiltrating malignancies and bone marrow aplasia; where steroid therapy can adversely affect their diagnosis and treatment.[4]

METHODS

The main objective was to study the clinico-morphologic profile of immune thrombocytopenic purpura. The study design was a retrospective five-year (2015 January to 2019 December) record-based study conducted in Haematology lab, Paediatric wing of a tertiary health care centre in South India. The study commenced only after getting Institutional Ethical Committee clearance (HEC.No.04/74/2020/MCT dated 26/6/20). All children who were diagnosed as immune thrombocytopenic purpura by peripheral blood, bone marrow morphology and other clinical work up were selected for this study. The clinical history regarding type and duration of bleeding, preceding viral infection, vaccination history, other coexisting autoimmune conditions were analysed from the data recorded in the medical records and haematology lab registers. Also, other parameters like CBC values, biochemical results, peripheral blood picture results, bone marrow aspiration results and response to steroid therapy details were collected. The haematology analyser used in our laboratory is 3-part differential Mindray analyser. The morphology of peripheral blood and bone marrow were studied using Giemsa and Leishman stained air dried blood films. The collected data was entered in SPSS software (version 16.0) and results were analysed. For analysing correlation chi-square test was used.

Inclusion Criteria

All cases of primary and acute ITP cases who underwent bone marrow study in our paediatric haematology wing during 2015 to 2019 period were included.

Exclusion Criteria

Cases of secondary ITP, chronic ITP, and Cases with inconclusive bone marrow results were excluded from our study.

RESULTS

During the study period, clinical and morphologic profile of 174 cases of ITP were analysed of which 52 % of children were males (n = 91) and 48 % of children were females (n = 83). The age of children ranged between 3 months to 15 years of age. The distribution of cases according to age and sex is depicted in Figure 1. In our study 42 % (n = 74) of cases were seen in 1 - 5 years of age, followed by 35 % (n = 62) cases in > 5 to 10 year age range. Children aged more than 10 years constituted 9 % (n = 17) and those less than one year of age constituted 12 % (n = 21). Slight male predominance was noted in less than one year age group and more than 10 years of age.

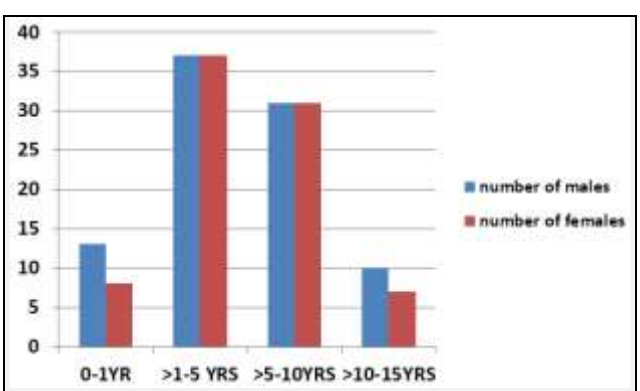

Figure 1. Distribution of Cases According to Age and Sex

The most common clinical presentation noted in our cases were petechial rashes, 71 % (n = 124), followed by ecchymoses and oral bleeding. Epistaxis, melaena, subconjunctival haemorrhage, increased menstrual bleed and haematuria were other less common clinical presentations noted in this study. The frequency and percentage of cases according to the clinical presentation is depicted in Table 1.

Clinical Presentation	Frequency	Percentage
Petechiae purpura	124	71
Ecchymosis	23	13
Oral / gum bleeding	12	7
Epistaxis	7	4
Melaena	3	1
Subconjunctival haemorrhage	3	2
Increased menstrual bleed	1	0.5
Hematuria	1	0.5
Total	**174**	**100**

Table 1. Distribution of Cases According to Clinical Presentation

Preceding viral fever history was seen in 53 % cases (n = 92), while 6.8 % (n = 12) cases had coexisting infections and 1.7 % cases (n = 3) had history of bleeding following a vaccination episode. Clinical examination of patients revealed pallor in 7.4 % cases (n = 13), increased body temperature in 13 cases (7.4 %), significant lymphadenopathy in 6.3 % (n = 11) and splenomegaly in 1 % cases (n = 3).

The platelet count was assessed by haematology counter was confirmed by peripheral smear method also. The thrombocytopenia was graded as mild (10,000 – 75,000 cells / mm^3), moderate (75,000 – 20,000 cells / mm^3) and severe (< 20,000 cells / mm^3). Majority (74 %, n = 128) of children in this study had moderate thrombocytopenia with platelet counts ranging from 26,000 – 50,000 cells / mm^3. Those with severe thrombocytopenia constituted 21 % (n = 36) and mild thrombocytopenia 6 % (n = 10).

Isolated thrombocytopenia with normal counts and morphology of WBCs and RBCs was the most common peripheral blood morphology observed in ITP cases studied (67.8 %, n = 118). Thrombocytopenia with other pathological changes like hypochromic microcytic anaemia, eosinophilia, and normochromic anaemia were seen in 29, 12, 10 and 3 cases respectively. The analysis of the cases based on peripheral blood morphology is depicted in Table 2.

Peripheral Blood Morphology	Frequency	%
Thrombocytopenia	118	67.8
Hypochromic microcytic anaemia with thrombocytopenia	29	16.6
Eosinophilia with thrombocytopenia	12	6.8
Normochromic anaemia, thrombocytopenia	10	5.7
Leucopenia with thrombocytopenia	3	2
Leucoerythroblastic blood picture with thrombocytopenia	2	1.1
Total	**174**	**100**

Table 2 Distribution of Cases According to Peripheral Blood Morphology

The bone marrow morphology of all cases showed megakaryocyte proliferation in normal and hypolobated forms. Marked megakaryocyte clustering was noted in 40 % cases (n = 70). Marrow eosinophilia was observed in 24 % cases (n = 43). Bone marrow iron staining was done in all cases who had low haemoglobin / PCV with anaemic blood picture. The bone marrow iron staining was zero in 15 cases (9 %) and a diagnosis of ITP with iron deficiency anaemia was made in those cases. Myeloid hyperplasia was observed in 2 % cases (n = 4). The morphological changes observed in peripheral blood and bone marrow of ITP cases are depicted in figure 2.

The platelet count after steroid therapy / IVIG therapy in all cases diagnosed with ITP were analysed. Immediate response showing rise in platelet count within 72 hours were observed in 147 cases (84 %), whereas 14 % cases (n = 24) showed delayed response to treatment. Treatment response was absent in three children (1.7 %) who were referred for further evaluation.

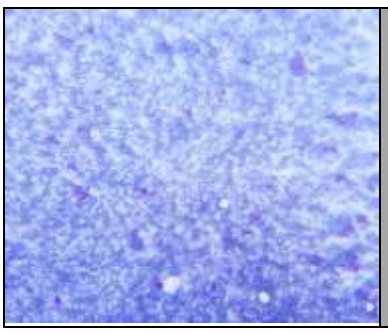

Figure 2A. Bone Marrow Aspirate Film 40X Magnification Showing Megakaryocyte Proliferation

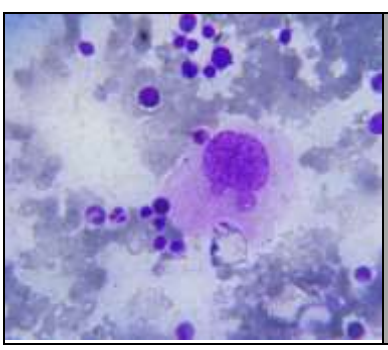

Figure 2B. Bone Marrow Aspirate Film 1000 X (Oil Immersion Objective) Magnification Normolobated Megakaryocyte

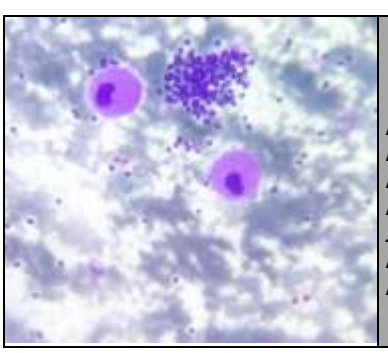

Figure 2C. Bone Marrow Aspirate Film 1000X Magnification (Oil Immersion Objective) - Hypolobated Megakaryocytes

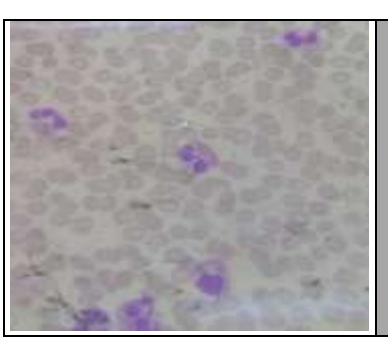

Figure 2D. Peripheral Blood Film 1000X Magnification (Oil Immersion Objective) – ITP Case Showing Eosinophilia

DISCUSSION

In our study, the peak incidence of ITP was noted between 1 year and 5 years of age, with male predominance during infancy (M: F = 1.62: 1) and in older children aged more than 10 years (M : F = 1.42 : 1). Literature review shows paediatric ITP can present in any age group but with peak incidence in 2 - 5 years of age, followed by a smaller peak in adolescence. Our study shows concordant results with

Kuhne et al's Intercontinental Childhood ITP study (ICIS) in 2540 paediatric patients which concluded equal sex predilection in all paediatric population with slight male predominance during infancy (M : F = 1.7 : 1).[3]

In our study, the most common presentation of immune thrombocytopenic purpura was petechiae and purpura (71 %) followed by ecchymoses (13 %). Bleeding from oral cavity, nostrils constituted only minor percentage in our study. Our observations are in concordance with Choi et al's and Bolton-Maggs et al's studies.[5,6] History of preceding viral infection was present in 53 % of the ITP cases, concomitant viral infections were present in 6.8 % cases in our study which is in concordance with Boltan Maggs study which showed similar history in 57 % cases.[6] A review study by Blanchatee et al showed significant number of ITP cases have preceding viral infection history[7] Lo C et al study reported positive history of infection in 57.1 %.[8] Vaccination history was seen in 1.7 % cases in present study while in Miller et al study incidence of developing ITP within six weeks of immunization was 1 in 22300 doses.[9] Mantadakis, Farmaki and Buchnan study concluded the incidence of MMR associated ITP ranged from 0.087 to 4 cases per 100000 vaccine doses.[10] Drug induced triggered immune response has been postulated as the cause of this condition.[11,12] Other clinical signs like hepatosplenomegaly, lymphadenopathy pallor etc are rarely recorded in literature. Blanchette et al describes small cervical lymphadenopathy can occur in young children, and slightly palpable spleen may be present in 5 % to 10 % of children with ITP. In our study other than few patients having fever (7.4 %), pallor (7.4 %), lymphadenopathy (6.3), mild splenomegaly (1 %); all other children showed no significant clinical findings.[7]

In our study the grade of thrombocytopenia was taken as an indicator of disease severity. In our study 74 % of children showed moderate levels of thrombocytopenia, 21 % showed severe thrombocytopenia and 6 % showed mild thrombocytopenia. The results are concordant with the observations made by Maria Elena et al in paediatric ITP cases in Mexico which also described predominant cases with childhood ITP with petechiae and purpura had platelet count above 20,000 cells / mm^3.[13]

Isolated thrombocytopenia is the common peripheral blood finding in ITP. But associated iron deficiency anaemia due to bleeding episodes can cause hypochromic microcytic picture in some cases. In the present study isolated thrombocytopenia was observed in 67.8 % of cases and 29 % of cases showed additional hypochromic microcytic anaemia picture. Eosinophilia is a common association of ITP recorded in literature. Blanchette et al described eosinophilia as a common finding in ITP cases.[7] Another study conducted in a tertiary health care centre of South India by Srinivasan Thyagarajan and Omana showed eosinophilia in 23.3 %, relative lymphocytosis in 30 % and neutrophilia in 26.6 % of paediatric ITP cases.[14] Though the reasons are obscure, many researchers have observed this association in ITP cases.[7] Concomitant infections can result in leucopoenia, atypical lymphocytes, neutrophilic leucocytosis and leucoerythroblastic blood picture.

In our study 100 % cases showed moderate to marked megakaryocyte proliferation with 40 % cases showing megakaryocyte clustering. Megakaryocytes were seen in normolobated, hypolobated and dwarf forms. Megakaryocyte proliferation with nongranular psuedoplatelet formation was noted in Limarzi and Schleicher studies while Dameshek and Miller reported diminished megakaryocyte granularity with degenerative changes and diminished platelet production.[15,16] Decreased megakaryocyte granularity, ploidy and smooth nonbudding cellular forms with increased immature forms was observed by Valentine.[17] Harker concluded that the megakaryocytes numbers in ITP cases are more numerous and larger than the control population.[18]

In our study a diagnosis of coexisting iron deficiency anaemia was made in 9 % cases due to grade zero bone marrow iron studies. Iron deficiency anaemia is a very common nutritional deficiency seen in our country. Though chronic bleeding in thrombocytopenia can result in iron deficiency anaemia, pre-existing nutritional deficiencies before the onset of ITP is not clear in our cases. Moreover, literature review shows severe thrombocytopenia can occur as a consequence of iron deficiency anaemia. Thrombocytopenia in iron deficiency anaemia findings were observed by Lopas et al and Perlman et al.[19,20] All these studies reported dramatic improvement of both platelet count and haemoglobin values after iron therapy.

The treatment options in ITP include steroids and IVIG in majority of cases while immunosuppressive drugs, monoclonal antibodies and splenectomy will be tried in refractory cases or those present with life threatening bleeding manifestations like intracranial bleed. In our study the response to steroid / IVIG therapy of all diagnosed cases was monitored during hospital stay period with repeated blood platelet counts. Separate response to steroid, IVIG and combination therapy was not assessed in our study. Immediate response showing significant elevation in platelet count within 72 hours were observed in (84 %). Watt reported out of 256 ITP cases treated with steroids, 235 showed good response.[21] Beck et al's study reported IVIG give rapid recovery in 80 % cases which is better than corticosteroid therapy.[22] Sinan et al conducted study in 260 acute ITP patients; out of 247 people who received therapy 180 patients were treated with high dose steroids, 32 patients with ordinary steroid dose, 20 with IVIG and 11 patients with combination of steroid and IVIG. The response in high dose steroid was 80 % (n = 145), ordinary steroid was 78 % (n = 25), IVIG was 80 % (n = 16) and for combination therapy was 82 % (n = 9).[23] In our study delayed response was noted in 14 % cases. Treatment response was absent in 3 cases in our study. George et al reported 58.3 % cases of paediatric ITP in his study had delayed response to therapy with complete response only at six month period and 6.6 % cases had no response to therapy at all.[24] The treatment response of the cases by grading platelet count into non severe and severe grade showed by chi-square test showed no significant correlation (p value > 0.05). Our findings are in concordance with the observations made by Sinan et al and another study conducted in South India.[23,14]

CONCLUSIONS

Immune thrombocytopenic purpura is a very common paediatric disease in our population. Though benign and a self-limiting condition, it prompts parents to seek immediate medical attention due to bleeding episodes associated with it. Immune thrombocytopenia is a diagnosis of exclusion and hence clinician needs to evaluate all other causes of bleeding before starting treating the case. Though bone marrow examination is not indicated in all cases of ITP, it is done in all cases of suspected ITP in many centres to exclude any other underlying bone marrow pathology. Paediatric cases of ITP usually present following viral infections or vaccination, with worrisome bleeding episodes, petechiae, ecchymosis or purpura. The platelet count can range from mild to moderate grades of thrombocytopenia. Other than bleeding spots, significant clinical findings are absent in ITP cases. Though isolated thrombocytopenia is the most common finding, eosinophilia and coexisting anaemia can be seen in cases. Bone marrow examination helps in excluding the main differential diagnosis in cases presenting with thrombocytopenia and it mainly categorizes thrombocytopenia into hypo proliferative and destructive thrombocytopenia. Peripheral thrombocytopenia with compensatory hyperplasia of megakaryocytes in the bone marrow with absence of other established autoimmune diseases, splenomegaly and other causes of peripheral destruction confirms the diagnosis of ITP. The treatment response of paediatric patients to steroid / IVIG is good and only few patients remain unresponsive to therapy.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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