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STUDY OF CLINICAL MANIFESTATION OF IMMUNE THROMBOCYTOPENIC PURPURA IN PAEDIA AGE GROUP

Paediatrics

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ABSTRACT

BACKGROUND: Immune Thrombocytopenic purpura (ITP) is a common clinical condition having varied presentations. It could be asymptomatic to devastating serious clinical haemorrhages. **MATERIAL AND METHODS**: This is Cross sectional study, Based on a proforma details about children with ITP presenting to our hospital at, Narayan medical college and Hospital, Jamuhar Sasaram Rohtas, Bihar. Convenience sampling was done to meet the sample size. **CONCLUSION:** Our study had a higher incidence of ITP presenting to the hospital. Higher proportion of them presented with severe bleeding.

KEYWORDS

Immune thrombocytopenia, bleeding, Nordic score.

INTRODUCTION

Immune thrombocytopenia is mediated by platelet antibodies that accelerate platelet destruction and inhibit their production. Most cases are considered primary (hereafter designated ITP), whereas others are attributed to coexisting conditions (secondary ITP). Immune thrombocytopenic purpura (ITP) is an autoimmune bleeding disorder in children, presenting itself with petechiae, easy bruising, and mucosal bleeding (1). ITP is characterized by isolated thrombocytopenia (platelet count of <100,000/ul with normal white blood cell count and haemoglobin. (1-3), variability in natural history and response to therapy suggests that ITP comprises heterogeneous disorders that eventuate in the production of platelet auto antibodies. Insights from secondary forms (e.g., coexisting immune deficiency and molecular mimicry after infection) suggest that platelet-reactive antibodies arise through diverse mechanisms. ITP can occur across all the age groups; however the peak age is between 2-5 years. (5) Childhood ITP has an estimated incidence of 4.0 – 5.3 per 100000 children. (2) It is considerably higher than the incidence of adult ITP. In ITP the presentations tend to be varied in nature and various classifications have been proposed to describe the same. Many patients have either no symptoms or minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal haemorrhage (GI), extensive skin and mucosal haemorrhage, or intracranial haemorrhage (ICH). The classic incidence described for severe bleeding and intracranial bleeding is about 3% and 0.5% respectively. ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (> 12 months' duration from the time of symptoms). (7) Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months (2)Various terminologies have been used to explain the course and presentations of the disease. The standardization of this has been proposed by the international working group, which gave terminologies to various presentations (grades of bleeding), and natural course of the disease. The Nordic idiopathic thrombocytopenic purpura study data showed that morbidity occurred mainly in children with thrombocytopenia lasting >3 months, whereas, the risk period with platelet counts <20 · 109/l was short and the number of bleeding events were low in children with shorter disease duration. abrupt onset (weight 5), age <10 years (3), preceding infection (2), platelet count <5 ·109/l, wet purpura (1) and male gender (1). Numerous controversies have ensued during the past several decades regarding management of childhood ITP, including the need for a bone marrow aspirate to confirm diagnosis, the need for hospitalization for observation and initiation of treatment, and the requirement for drug therapy aimed at raising the platelet count to prevent haemorrhage. Full blood count reveals isolated thrombocytopenia with normal haemoglobin (Hb) level, white blood count (WBC) and normal peripheral blood smear. Initial management options for newly diagnosed childhood ITP include; observation only, the use of intravenous immunoglobulin (IVIG), steroids, anti-D immunoglobulin, various clinical presentations of ITP, highlighting the essential differences between acute and chronic ITP with regards to their presentation and severity of bleeding.

OBJECTIVES

Proportion of children presenting with moderate to severe bleeding in immune thrombocytopenic purpura at their first presentation. The relationship with platelet counts and severity of bleeding.

Review of Literature

Idiopathic thrombocytopenic purpura (ITP) is one of the most common causes of symptomatic thrombocytopenia in children.

Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder which is characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than $10X10^9$/L, and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.

Secondary ITP: All forms of immune-mediated thrombocytopenia except primary ITP. , prevalence, and natural history of ITP in children differ significantly from that of adult ITP. Childhood ITP has an estimated incidence of 4.0– 5.3 per 100,000 while adult ITP has lower incidence of 1.6 - 2.6 per 100,000. It is commonly seen between the age groups of 2-6years and rare below 1 year. ITP in children affects males and females equally, but in infancy males are affected more frequently than females. (2, 5) Childhood ITP has an acute abrupt onset and is commonly preceded few weeks earlier by a viral illness or immunization, such as mumps, measles and rubella (MMR) vaccine (17). Fernington et al estimated the risk to be 1 in 24,000 doses of MMR vaccine (18). In a large multi-centre study by the International Childhood ITP Registry (ICIS), data was collected from 2031 children with ITP. There were 136 centres from 38 countries participating in the study. Frequency of ITP reached a peak during the spring and a nadir during autumn (19). ITP resolves within 6 months in up to 85 % of children with or without drug treatment. However, 25% of children may continue to have symptomatic ITP (20). the history of vaccination in past 6 weeks was analysed in a study by Farhangi H et al. Results showed that it did not have any effect on platelet count ($p = 0.28$), hemoglobin level ($p = 0.51$), and duration of hospitalization ($p = 0.51$). While on the other hand, ITP in children under 3-months was significantly associated with vaccination ($p=0.007$). Immune thrombocytopenia is mediated by platelet antibodies which accelerate the platelet destruction and inhibit their production. Most cases are considered primary, whereas others are attributed to coexisting conditions (secondary ITP). Insights from secondary forms suggest that platelet-reactive antibodies arise through diverse mechanisms. In addition, to this even environmental and genetic factors may impact platelet turnover, the propensity to bleed, and response to ITP directed therapy. (4) This diversity of autoimmune mechanisms involves antibodies, B cells, and T cells, which has been described by Douglas B. Cines Et al describing the tolerance check point defects in ITP. Auto-antibodies against platelet antigens are considered the diagnostic hallmark of ITP. In some patients, antibodies recognize antigens derived from a single glycoprotein while in others they recognize multiple glycol- proteins. (23) Opsonisation by the antibody not only accelerates the platelet clearance but it can also alter the platelet function and interfere with its production. Khellaf et al. reported a moderate correlation between a platelet count $< 20 \times 109$ L−1 and bleeding ($r = -0.40$; $P < 0.01$) (24). While on the other hand, Page et al.

did not observe any correlation between thrombocytopenia (< 30 × 109 L−1) and bleeding (35). Pansy et al. The diagnosis of ITP in children is essentially one of exclusion. In order to differentiate ITP from other conditions, medical history should include type and severity of bleeding, associated systemic symptoms, history of respiratory infections, recent live viral vaccine like MMR, medications, presence of bone pain/ swellings, and if any family history of bleeding disorders. bone marrow aspiration (BMA) is not required to establish the diagnosis of ITP and also is not necessary prior to steroid treatment. It should be done if there is bone pain, lymphadenopathy, hepatosplenomegaly, anaemia that is not explained by blood loss, or abnormally high or low WBC. The nature of presentation of a clinical entity such as ITP is quite varied in terms of age of presentation, site of bleeding, platelet counts and severity of bleeding. The course of the disease is also quite varied among these patients.

MATERIALAND METHODS

This is Prospective, observational study, Based on a proforma details about children with ITP presenting to our hospital at, Narayan medical college and Hospital, Jamuhar Sasaram Rohtas, Bihar. Pediatrics OPD/ wards/ PICU, Convenience sampling was done to meet the sample size.

INCLUSION CRITERIA – All children between 1-18 yrs with a clinical diagnosis of primary Immune Thrombocytopenic purpura (ITP).

EXCLUSION CRITERIA- Secondary causes of Immune thrombocytopenia as evaluated by the primary clinician.

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 scoring was done and subsequently followed up at 3 months and 6 months to look for duration of symptoms. Based on a similar study (3) looking at the proportion of various grades of bleeding, the sample size was calculated to estimate the proportion of moderate to severe bleeding in our ITP population with: Relative precision: 30%Confidence interval: 95% Required sample size: 143.

RESULTS

After excluding the ones which had a secondary cause identified, the total primary ITP studied were 146. Among them based on the duration of symptoms (as per definitions) they were categorized into newly diagnosed, persistent and chronic ITP.

Number of children in newly diagnosed, persistent and chronic ITP recruited in the study

Sl No	Type	Number
1	Newly diagnosed (acute)	54
2	Persistent	13
3	Chronic	79
4	Secondary causes	7

Age wise presentation in newly diagnosed ITP

Sl No	Age	Number	Percentage
1	1-5	28	51.8%
2	6-10	18	33.4%
3	>10	8	14.8%

Haematological parameters at presentation in newly diagnosed, persistent and chronic ITP

	ACUTE ITP (N=54)	PERSISTENT ITP (N=13)	CHRONIC ITP (N=79)	P VALUE
Hb (g/dl)	10.7 ± 2.3	10.9 ± 1.9	11.4 ± 1.8	0.0515
Total count	11858 ± 261	11596 ± 342	10849± 543	0.1045
Mean Platelet count	14700 ± 1552	17425 ± 1789	16645± 2475	0.0675

Platelet count and severity of bleeding in newly diagnosed ITP

SEVERITY	PLATELETS <20000/dl	PLATELETS >20000/dl
Mild	67.7%	32.3%
Moderate	72.2%	27.8%
Severe	40%	60%

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

Platelet count and severity of bleeding in chronic ITP

SEVERITY	PLATELETS <20000	PLATELETS >20000
Mild	31.2%	68.8%
Moderate	55.8%	44.2%
Severe	71.4%	28.6%

There is no statistically significant difference. (p- 0.0857)

DISCUSSION

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. (2, 48-49) 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 146 primary ITP, out of which, 37% were acute ITP, 9% remained persistent in the time frame of the study and the remaining 54% were chronic ITP presenting to our hospital. ITP typically presents among children between 1 to 10 years of age group, with a peak incidence between 2 to 7 years of age and rare below 1 year (2,5). While in our study we had 85% all acute ITP presenting in this age group, 84.7 % of all persistent and 74.7% of all chronic ITP during their first presentation presenting in age. In a study of 2031 children who had acute ITP, the mean age at presentation was 5.7 years (19), similar to our study. There is no sex predilection among children with ITP, even though among infants there are more boys than girls presenting with ITP (6,19,42,50,51). In some cohorts, there is a slight predilection to boys across age groups among acute ITP. 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. Bleeding in ITP is classified as mild, moderate and severe based on Bolton-Maggs and Moon bleeding grade classification which includes- Mild bleeding is that involves the skin or mild epistaxis, Moderate bleeding is more severe skin bleeds with troublesome epistaxis or menorrhagea. 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. 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 (58). Butros et al. 2003 (58) reviewed 75 published cases of ICH with ITP from 1954 to 1998. Sixty-two cases ranged from 6 months to 20 years of age. There is a prior history of infection present in about 60% of paediatric cases of ITP (19, 56) . 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. Platelets are critical for maintaining vascular integrity. They provide the surface for coagulation proteins and adhere to the vessel wall at sites of endothelial injury. Based on radio-labelled platelet survival studies in normal volunteers and in thrombocytopenic patients, it is estimated that approximately 7-8 10^9/L platelets are required to maintain vascular hemostasis. 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 a predicted spontaneous remission rate 61% after 15 years (67) and 63% remission in another series(68). a scoring system named NORDIC SCORE was designed by Edslev et al, in 2007 after his study

in a cohort of ITP children from the Nordic countries. 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. unless with atypical features defined as those who have prolonged fever, bone pains and unexplained anaemia, neutropenia or macrocytosis, lymphadenopathy, hepatospleenomegaly.

CONCLUSION

ITP is a common cause for thrombocytopenia in children. It is commonly seen in the age group of 1-10 years with equal distribution among boys and girls. Clinical profile of acute and chronic ITP in our study was similar to the data available from studies in India and worldwide. The grades of bleeding however showed increased proportion of children with severe bleeds in our cohort, attributing to the study centre being a referral tertiary care centre. There was no statistically significant correlation noted between the platelet count and severity of bleeding among acute and persistent ITP, however there was a trend towards increased severe bleeds in chronic ITP with lower platelet counts.

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