Original Article

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A Prospective Study to Evaluate the Etiopathological Profile Represents the Various Causes of Thrombocytopenia and Their Comparison among Different Age Groups & Sex

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Abstract

Background: Platelet disorders are commonly encountered clinical problems that may lead to severe bleeding episodes requiring transfusion or hospitalization. Present study is focussed on determining etiopathological profile of thrombocytopenia which is a quantitative platelet disorder. **Subjects and Methods:** The data for this study was collected by 100 patient evaluation was done by detailed history taking, Clinical examination and relevant investigations using a proforma specially designed for this study in Santokba Durlabhji Hospital, Jaipur. EDTA blood samples were taken for CBC, Hb, APC, estimation and citrated blood in 1:9 dilution were taken for PT & PTTK estimation. **Results:** In our study incidence of petechiae, ecchymosis & malena was does not depend on age group, but epistaxis & Haemetemesis depends on age group. Here using Pearson Chi-Square test we conclude p value to be significant ($p<0.05$) thus supporting the basis of this study that incidence of various etiologies of thrombocytopenia varies according to age group. Male & female ratio was 2.12:1was seen in this study. **Conclusion:** This study is to provide a firm knowledge of the major causes of thrombocytopenia and to form a broad differential diagnosis. Present study infers that various etiologies can be attributed to specific age groups. Moreover different manifestations of thrombocytopenia also vary according to age group.

Keywords: Thrombocytopenia, Etopathological, Platelet disorders, Age group.

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Introduction

Haemostasis is a complex host defence mechanism which requires the close interaction of platelets, coagulation factors, and endothelial cells. Congenital or acquired abnormalities of any of these components can lead to a bleeding disorder which may range from trivial to life threatening.[1]

Platelet disorders are commonly encountered clinical problems that may lead to severe bleeding episodes requiring transfusion or hospitalization. Platelet abnormalities may be physiologically characterized as quantitative or qualitative in nature.[1]

Present study is focussed on determining etiopathological profile of thrombocytopenia which is a quantitative platelet disorder. Thrombocytopenia refers to reduction in platelet count to < 150 x 109 /L.[2] Platelets are non-nucleated cellular fragments produced by megakaryocytes within the bone-marrow and other tissues that circulate in the blood as discs with a volume of about 7-9 fL (avg 7.5 fL), 14 times smaller than erythrocytes. They have a lifespan of 10-14 days.

In general, the etiology of thrombocytopenia can be classified into disorders associated with decreased production, increased destruction, sequestration, or loss.3 Few common causes among neonates are congenital infection, placental insufficiency, perinatal asphyxia, DIC and late onset sepsis.[2]

A bleeding time may also be helpful, as it may be disproportionately prolonged for the platelet count, suggesting platelet dysfunction. A bone-marrow biopsy and aspirate is required to assess platelet production. Coagulation tests should also be done to rule out an accompanying coagulopathy such as disseminated intravascular coagulation (DIC).Bone-marrow damage commonly results in a decrease in all three marrow cell lines, resulting in varying degrees of cytopenias and marrow aplasias. This is seen, in the form of aplastic anemia, during/after exposure to drugs (cancer chemotherapy, heparin, chloramphenicol), toxins, radiation, infections, thymomas, and unexplained causes.

Recent years have witnessed an upsurge in patients with thrombocytopenia resulting from a number of varying etiologies. Thrombocytopenia in children warrants serious consideration and investigation. This study is to provide a firm knowledge of the major causes of thrombocytopenia and to form a broad differential diagnosis, so that it will be

clearer when to consider a rare etiology. A brief categorization of causes of thrombocytopenia and their relation with different age groups of pediatric population and sex is included. The causes, treatment modalities, and outcomes of thrombocytopenia have to be evaluated for providing better care and follow-up. Therefore present study was undertaken to determine etiopathological profile of patients suffering from thrombocytopenia in paediatric age group.

Subjects and Methods

The data for this study was collected by 100 patient evaluation was done by detailed history taking, Clinical examination and relevant investigations using a proforma specially designed for this study in santokba durlabhji hospital, Jaipur. Ethical clearance was obtained from the institutional ethical committee.

Inclusion criteria:

- Patients with documented thrombocytopenia
- Of the above, those consenting for required investigations and history taking were included in the study.

Exclusion criteria:

- Subjects not providing consent.
- Subjects outside paediatric age group(0-15Yrs)

Investigation Techniques

Blood investigation

Blood samples were collected from peripheral vein by a 21 gauge needle with 5 ml syringe for all laboratory investigation that were needed for diagnosis and management.

EDTA blood samples were taken for CBC, Hb, APC, estimation and citrated blood in 1:9 dilution were taken for PT & PTTK estimation. The blood was thoroughly mixed with the anticoagulant by inverting the container several times. The samples were brought to the laboratory as soon as possible.

Blood counts

Total leukocyte count were done by improved neubauers chamber using turks fluid and WBC pipette and was examined under light microscope. CBC is done by automatic analyzer.

PBF was made on glass slide and stained with Leishman Stain. After air drying examination under oil emersion lens was done. Platelet counts was also done through PBF.

Bleeding Time (BT)

It was done by Dukes method

After clearing the lobe of ear or tip of finger with alcohol and let it dry. Glass slide is placed behind ear lobe and firmly in place. Pierce the lob of ear by a firm stroke against the glass slide. Start the stop watch when the stab was made. Bleeding of the wound should be allowed to proceed without pressure and blood is allowed to drop on filter paper. Filter paper should be moved so that each drop will fall on a fresh area. When the bleeding slows wound in touched gently with the fresh area of the filter paper at 30 seconds intervals. When blood no longer stains the filter paper the watch is stopped and the time is recorded.

- Normal value : Upto 6 minutes (N)
- 6-10 minutes (border line)
- > 10 minutes (abnormal)

Platelet count

Preferably use venous blood for platelet count. The blood is diluted in 1% ammonium oxalate stored at 4°C which haemolyse RBC.

Take blood in RBC pippet upto mark one and dilute with platelet diluting fluid upto mark 101.

Shake and keep for 15-20 minutes. Charge the Neubauer chamber from the RBC pippet after thoroughly shaking and discarging few drops. Keep the Neubauer chambers in a moist petridish for 15-20 minutes to give time for platelets to settle. Then count the platelets in 5 RBC counting chambers.

Calculation

Counts per litre =	No. of cell counted	x100x106
	Volume counted (/L)	

Thus if N is the number of platelets counted in an area of 1mm2 the number of platelets per litre of blood is N x 10 x dilution factor x 106 = N x 1000 x 106

Normal value=- 1.5- 4.5 lacs/cumm

Prothrombin Time (PT)

The test measures the clotting time of plasma in the present of an optimal concentration of tissue extract (thromboplastin) and then indicates the overall efficiency of extrinsic pathway.

Method

1.8 ml of venous blood is taken in P.T. vial containing 0.2 ml odium citrate as an anticoagulant. This is mixed through and centriguged to separate the plasma. 0.2 ml of plasma is taken in a coagulation tube and put at 37°C in a coagulation timer. To this add prewarmed 0.2 ml thromboplastin. Start the stop watch and note the coagulation time. This was run with a control (Normal pooled plasma) and test were run into duplicates.

Control value 12-14 seconds.

Partial thromboplastin time with Kaolin (PTTK)

The test measures the clotting time of plasma after the activation of contact factors but without added tissue thromboplastin, and so indicates the over all efficiency of intrinsic pathway.

Method

1.8 ml of venous blood is taken in P.T. vial containing 0.2 ml sodium citrate as an anticoagulant. This is mixed thorough and centrifuged to separate the plasma. Take 0.1 ml of plasma in a coagulation tube and add 0.1 ml cephaloplastin (Merk, it is a phospholipid with Kaolin). Now put at 37°C in a coagulation timer for 10 minutes. To this mixture add prewarmed 0.1 ml calcium chloride (0.025 m mol/L) exactly after 10 minute, stop watch is started. Recorded the time taken for the mixture to clot. This was run with control normal pooled plasma and test were run into duplicates.

Results

In our present study maximum distribution of petechiae, epistaxis & Haemetemesis was in 8-11 years of age group, but ecchymosis in 12-15 years of age group and Malena in 0-3 years of age group. As we see that distribution of cases with bleeding manifestation according to different age group is similar which is tested by Pearson Chi-Square test at p value 0.05.So in our study incidence of petechiae, ecchymosis & malena was does not depend on age group, but epistaxis & Haemetemesis depends on age group [Table 1].

Here using Pearson Chi-Square test we conclude p value to be significant ($p<0.05$) thus supporting the basis of this study that incidence of various etiologies of thrombocytopenia varies according to age group [Table 2].

In this study we observed that male & female ratio was 2.12:1 [Table 3].

Table 1: Age wise distribution of study population according to presence of various bleeding manifestations

Age groups	Petechiae		Ecchymosis		Epistaxis		Hemetemesis		Malena	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
0-3 years	71.4%	28.6%	42.9%	57.1%	21.4%	78.6%	7.1%	92.9%	42.9%	57.1%
4-7 years	72.2%	27.8%	44.4%	55.6%	27.8%	72.2%	5.6%	94.4%	16.7%	83.3%
8-11 years	91.7%	8.3%	33.3%	66.7%	75.0%	25.0%	33.3%	66.7%	16.7%	83.3%
12-15years	83.3%	16.7%	66.7%	33.3%	50.0%	50.0%	16.7%	83.3%	16.7%	83.3%
Total	78%	22%	44%	56.0%	40.0%	60.0%	14.0%	86.0%	24%	76.0%
Chi-square test	0.239 (NS)		0.305 (NS)		0.0001 (S)		0.013 (S)		0.056 (NS)	

Table 2: Distribution of definitive diagnosis according to age groups

S. No.	Diagnosis	0-3 years N (%)	4-7 years N (%)	8-11 years N (%)	12-15 years N (%)	Total N (%)
1	ITP	4 (11.76)	16 (47.05)	6 (17.64)	8 (23.52)	34 (100.0)
2	Neonatal Thrombocytopenia a/w PIH	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
3	Neonatal sepsis	3 (100.00)	0 (00.00)	0 (0.0)	0 (0.0)	3 (100.0)
4	Enteric fever	2 (50.0)	0 (0.0)	2 (50.0)	0 (0.0)	4 (100.0)
5	Malaria	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
6	Leukemia	4 (22.22)	10(55.55)	4 (22.22)	0 (0.0)	18 (100.0)
7	Dengue	3 (15.79)	6 (31.57)	8 (42.10)	2 (10.52)	19 (100.0)
8	Aplastic Anemia	2 (20.0)	0 (0.0)	6 (60.0)	2 (20.0)	10 (100.0)
9	HUS	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
10	DIC	5 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)
	Total	28 (28.0)	34 (34.0)	26 (26.0)	12 (12.0)	100 (100.0)

Table 3: Distribution of study population according to SEX

Sex	Frequency(n)	Percentage(%)
Male	68	68.0
Female	32	32.0
Total	100	100.0

Discussion

Bleeding is an important sign that warrants recognition, evaluation and intervention. It is arrested normally by the normal Haemostatic response. In general three organs or tissues are primarily involved in normal haemostatic mechanism. They are bone marrow: megakaryocytes, which produce the blood platelets and in turn furnish the thromboplastin; the liver; which supplies prothrombin, fibrinogen and other clotting factors; and blood vessels, with their endothelial function and capillary reactions.

The various etiologies are presented by known disease entities, grouped by age, and described as they would occur and be considered in a realistic clinical setting. A brief categorization of causes of thrombocytopenia by mechanism, notably abnormal platelet production, platelet destruction, or sequestration, is included.

The mean age was observed to be 6.16±3.8 years. The present study shows the maximum distribution of cases attributing to Idiopathic thrombocytopenia (32%), followed by Dengue (19%), leukaemia (18%), Aplastic anaemia (10%), DIC (7%), Enteric fever (4%), neonatal sepsis and thrombocytopenia due to maternal PIH (3.0%) and minimum cases of definitive diagnosis such as malaria & Haemolytic uremic syndrome.

Mostly patients have petechiae (78%) followed by ecchymosis (44%), epistaxis (40%), melena (24%) and hemetemesis (14%) as the presenting symptom. In our maximum incidence of idiopathic thrombocytopenic patients were found in age group 3-6 years constituting 47%. In age group 0-3 years it was 17.6% and in 7-9 years it was 23%.

In age wise distribution of leukemia incidence was same between 0-3 years and 3-6 years group constituting about 33% overall in each group. In the 7-9 years age group it was 22%. Regarding age wise distribution of thrombocytopenia associated with idiopathic aplastic anemia, maximum incidence was found in age group 9-14 years - 60%.

In 6-9 year group it was 20% and in 0-3 year group it was 20%. High incidence of hypoplastic / aplastic anaemia in older age group may be attributed to need of long-term exposure of causative agent on bone marrow eg. viruses, radiation, chemicals and drugs to produce their effect.

In septicemia and disseminated intravascular coagulation group, highest incidence was in 0-3 years group - 66%. In 3-6 years group it was 22% and in 9-14 years group it was

11%. In dengue fever the highest incidence was found in age group 6-9 years- 50%.

According to a study by Alam MM.4 (2014) the mean age at the time of presentation of ITP was 6.1±3.8 years. A total of 34(35.8%) patients had history of preceding illness. Regarding clinical presentations, bruises 81(85.3%), petechial rash 75(79%), epistaxis 23(24%) were common. It is important to note that the clinical manifestations of thrombocytopenia vary with patient age. Older patients have more severe and rare bleeding manifestations, such as GI bleeding and possibly intracranial hemorrhage secondary to co-morbidities such as hypertension.

Regarding the clinical manifestation of present study, the maximum no. of patients were noted to have fever (54%) followed by hepatomegaly (44%) & Splenomegaly(42%). In evaluating a patient with thrombocytopenia, it is essential to obtain a complete past medical history and family history, to review the blood count, and to review the smear to examine the morphology of the platelets and assess for the possibility of ‘‘artifactual’’ thrombocytopenia.

The relevance of thrombocytopenia in the individual patient is variable and depends on the clinical presentation However, the presence of thrombocytopenia can aggravate surgical or traumatic bleeding or prevent the administration of effective treatment for several conditions (eg, antiviral therapy for chronic hepatitis C virus infection or cancer chemotherapy). In other situations, a low platelet count is the only initial manifestation of an underlying disorder that poses greater risks than thrombocytopenia itself (eg, HIV infection or myelodysplastic syndromes) or is an important marker of disease activity (eg, thrombotic microangiopathies).

Major causes of neonatal thrombocytopenia in our study were found to be sepsis and thrombocytopenia due to pregnancy induced hypertension in mother. This study shows that the causes of neonatal thrombocytopenia may show variations with respect to time and the prevalence, complications, and risks of thrombocytopenia may be lowered by eliminating preventable factors. According to the study by Eslami Z et al,[5] (2013) thrombocytopenia is the most common hematological abnormality which is encountered in the neonatal intensive care unit (NICU). Thrombocytopenia was associated with sepsis, intrauterine growth retardation sepsis, asphyxia, GDM, maternal hypertension and prematurity. There was no relation between occurrence of thrombocytopenia and gender.

Similarly Bhat YR et al,[6] (2008) found that higher percentage of thrombocytopenia was associated with male gender (47.7%), low birth weight (71.4%) and prematurity (67.4%). Severe thrombocytopenia was significantly associated with low birth weight (OR: 4.58; 95% CI: 0.98–21.3; p<0.03) and prematurity (OR: 2.52; 95% CI: 0.87–7.24; p<0.05).

Various studies have been conducted to establish etiology of thrombocytopenia in specific diseases and the correlation of bleeding manifestations with abnormal laboratory test values. Schexneider et al,[7] (2005) suggested that thrombocytopenia in dengue fever results from a complex mechanism involving platelet activation, procoagulant and anti coagulant arm of coagulation system, complement and cytokine activation. Platelet count does not correlate with clinical bleeding and symptomatic thrombocytopenia may require platelet transfusion.

Another study done by Alaei K et al,[8] (2003) evaluated the rate of thrombocytopenia (plateletcount<100000/microL) in170 HIV-infected patients. While 34 patients had thrombocytopenia, 3 had severe thrombocytopenia (platelet count < 20 000/microL). Although prevalence was similar in various stages of HIV infection (18.5%-22.5%), severe thrombocytopenia was in patients with CD4 T cell count < 200 cells/microL. There were no other associated conditions.

As per Fohlmeister I et al,[9] (1985) concluded that aplastic anaemia can thus be subdivided morphologically into two disease entities-namely, hypocellular myelodysplastic syndrome with a 23-82% risk of acute non-lymphatic leukaemia developing within three years, depending on how many variables associated with acute non-lymphatic leukaemia are present, and non-dysplastic myelohypoplasia.

Another study done by Sathiasekar AC et al,[10] (2015) on drug-induced thrombocytopenic purpura is a skin condition resulting from a low platelet count due to drug-induced anti-platelet antibodies caused by drugs. Drug-induced thrombocytopenic purpura should be suspected when a patient, child or adult, has sudden, severe thrombocytopenia.

Conclusion

Detailed evaluation of the etiopathological profile of thrombocytopenia on which present study is based certainly aids in forming differential diagnosis and executing appropriate management thus alleviating delay and chances of improper treatment. The causes, treatment modalities, and outcomes of thrombocytopenia have to be evaluated for providing better care and follow-up.

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