

Study of Etiological Factors of Thrombocytosis

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Abstract: ***Background and Aims:** thrombocytosis is classified according to origin as either essential (Primary) or reactive (Secondary). Essential thrombocytosis develops as a result of either a clonal bone marrow disorder or an abnormality in the biology of thrombopoietin. Secondary thrombocytosis is due to a variety of underlying conditions. Short lived secondary thrombocytosis is observed in conditions such as acute bleeding, trauma, major surgical procedures or after severe physical exertion. In contrast, secondary thrombocytosis associated with malignancy, chronic infection, iron deficiency or chronic inflammatory diseases may persist for a longer time. The distinction between clonal (essential) and reactive thrombocytosis is clinically relevant because the first is associated with thromboembolic and hemorrhagic complications, while the latter is not. To find out the etiological factors associated with thrombocytosis. **Methods:** After obtaining ethical committee approval, a hospital based, cross sectional observational case study was conducted. After applying inclusion and exclusion criteria, a total of 152 patients were enrolled. A 2 ml sample of a fresh whole blood of EDTA-K2 Anti coagulated was collected. The sample in the EDTA were transported manually at room temperature to the laboratory and analyzed to determine Platelets, between one to three hours after sampling using Sysmex KX 21 cell counter. High Platelet counts were confirmed by repeating the test at 48 hours later. After two sequential high Platelet counts, a peripheral blood smear examination of study subject done to reconfirm high Platelet count by a qualified faculty of Pathology department posted in hematology lab. **Results:** In present study out of 152 children, 151(99.34%) children have secondary thrombocytosis while 1(0.66%) children have primary thrombocytosis. Respiratory system disease having secondary thrombocytosis were 52(34.44%), gastro-intestinal system disease having secondary thrombocytosis were 33(21.85%), central nervous system disease having secondary thrombocytosis were 23(15.23%) and renal system disease having secondary thrombocytosis were 18(11.92%), infectious disease having secondary thrombocytosis were 12(7.95%), Hematological system disease having secondary thrombocytosis were 6(3.97%), systemic disease were 5(3.32%), endocrine disease 1(0.66%), biotinidase deficiency 1(0.66%). Respiratory diseases were the commonest cause of secondary thrombocytosis in children. **Conclusions:** In our study almost all thrombocytosis cases were having secondary thrombocytosis (reactive), only 1 case have primary thrombocytosis. Four common systems in children having secondary thrombocytosis were respiratory system (34.44%), gastro-intestinal system (21.85%), central nervous system (15.23%) and renal system (11.92%). Respiratory diseases were the commonest cause of secondary thrombocytosis in children.*

1. Introduction

- Platelets or thrombocytes are small colourless, non nucleated and moderately refractive bodies. These formed elements of blood are considered to be the fragments of cytoplasm.¹ The normal platelet count is $150-450 \times 10^9 /L$. Thrombocytopenia refers to a reduction in platelet count to $<150 \times 10^9 /L$. Thrombocytosis refers to a platelet count above the $450 \times 10^9 /L$ in the circulating blood.²
- Recently, with the wide spread use of the electronic cell counters and the subsequent availability of a platelet count as part of a routine complete blood count, thrombocytosis is more often observed as an unexpected finding. Thus, an elevated platelet count has become an important clinical problem for differential diagnosis.³
- Thrombocytosis is classified according to origin as either essential (Primary) or reactive (Secondary). Essential thrombocytosis develops as a result of either a clonal bone marrow disorder or an abnormality in the biology of thrombopoietin. Reactive thrombocytosis, on the other hand, occurs as a results or stimulation of megakaryopoiesis due to several conditions such as infection, tissue injury or anemia.⁴
- Secondary thrombocytosis is due to a variety of underlying conditions. Short lived secondary thrombocytosis is observed in conditions such as acute bleeding, trauma, major surgical procedures or after severe physical exertion. In contrast, secondary thrombocytosis associated with malignancy, chronic infection, iron deficiency or chronic inflammatory diseases may persist for a longer time⁵
- Thrombocytosis of childhood is mostly reactive (Secondary). It was reported that many markers of the

acute phase reaction, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are significantly elevated in patients with reactive thrombocytosis.

- The main interest of distinction between reactive and primary thrombocytosis resides in the increased incidence of thrombo-hemorrhagic complications and progress to acute leukemia in the later group. In rare individual cases it may be very difficult to differentiate between essential and reactive thrombocytosis. The distinction between clonal (essential) and reactive thrombocytosis is clinically relevant because the first is associated with thromboembolic and hemorrhagic complications, while the latter is not.³

2. Methods

- The Present study has been conducted in the department of Pediatric medicine, SPMCHI, SMS Medical college Jaipur, from June 2014 to July 2015, After obtaining approval from the institutional ethics committee of SMS Medical College Jaipur. This study is a hospital based, cross sectional observational case study. Written consent was obtained by parents of all enrolled children. A predesigned proforma was used for history and data collection.
- After applying inclusion and exclusion criteria, a total of 152 patients were enrolled. All children aged upto 18 years in whom thrombocytosis (Platelets $>450 \times 10^9 /L$) were identified during routine blood investigations for study.
- A 2 ml sample of a fresh whole blood of EDTA-K2 Anti coagulated was collected. For sample collection the skin

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surface was wiped with spirit, Iodine and then with spirit. The spirit was allowed to air dry and then using a 23G needle. The sample in the EDTA were transported manually at room temperature to the laboratory and analyzed to determine Platelet indices between one to three hours after sampling using Sysmex KX 21 cell counter.

- High Platelet counts were confirmed by repeating the test at 48 hours later. After two sequential high Platelet counts, a peripheral blood smear examination of study subject done to reconfirm high Platelet count by a qualified faculty of Pathology department posted in hematology lab SPMCHI SMS Medical College Jaipur.
- Children in whom thrombocytosis was identified included in the study. Presenting symptoms & signs with which these children admitted to the hospital were filled in the the structured and prevalidated proforma. History of blood transfusion in the past one week, Hb, WBC, TLC and Platelet counts as given by the automated blood cell analyzer were noted. Peripheral blood smear and other relevant investigations done to establish the diagnosis were also noted.

Inclusion criteria

- Patients having thrombocytosis($>450 \times 10^9/L$).
- Age upto 18 years.

Exclusion criteria

- Not willing for study (Refusal for study by patients or parents).
- Recent blood or platelet transfusion (within one week).

Statistical Analysis Method

- Data entry and analysis was performed with Microsoft excel, Primer and statcal software. The qualitative data was expressed in proportion and percentage while the quantitative data was expressed in mean and standard deviation. The differences in means were analyzed using student t-test and P value of <0.05 was considered significant.

3. Results

- A total of 152 children, 151(99.34%) children have secondary thrombocytosis while 1(0.66%) children have primary thrombocytosis. So almost all cases of thrombocytosis were reactive or secondary in nature.
- In 152 study subjects, 71.05% children have mild thrombocytosis, 19.08% children have moderate thrombocytosis, 3.29% children have severe thrombocytosis and 6.58% children have extreme thrombocytosis.
- Maximum number of children with thrombocytosis were in the age group 1month-1 year (41.45%) closely followed by >1 year-5 years (39.47%). Thrombocytosis was more common in male children (67.11%). Thrombocytosis was proportionately distributed among children of all major religions (Hindus, Muslims and

sikh). Thrombocytosis was more commonly observed in Hindu community (80.92%). The relatively higher proportion of thrombocytosis observed in muslims (17.76%) as compare to population composition of muslims (9.07%). Thrombocytosis was proportionately distributed among children of rural and urban locality. Children with thrombocytosis were more commonaly observed from rural (60.52%) residential area. The relatively higher proportion of thrombocytosis observed in urban residential area (34.87%) as compare to population composition of urban residential area (24.87%).

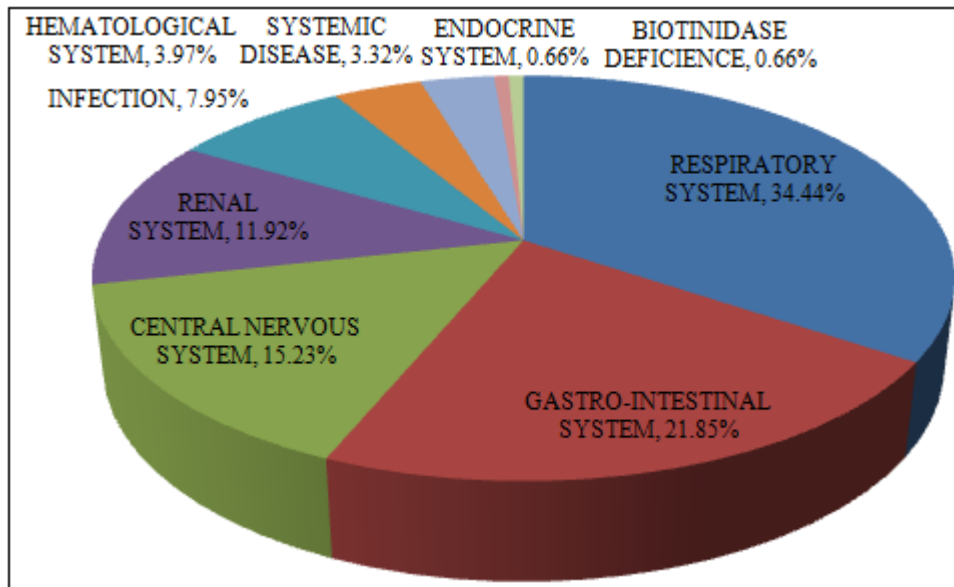
- No correlation was found between severity of thrombocytosis and hemoglobin level ($p > 0.05$).
- Three commonest systems observed in children with secondary thrombocytosis were respiratory system (34.44%), gastro-intestinal system (21.85%) and central nervous system (15.23%). Bronchopneumonia (51.92%) followed by pleural effusion (17.31%) was the commonest cause of thrombocytosis amongst respiratory diseases. Severe acute malnutrition (42.43%) followed by acute diarrhea (30.30%) were the commonest causes of thrombocytosis amongst gastro-intestinal diseases. Seizure disorders (30.44%) followed by pyomeningitis (21.73%) were the commonest causes of thrombocytosis amongst nervous system diseases.
- Frequent relapsing nephrotic syndrome (52.94%) was commonly associated with thrombocytosis than first relapse nephrotic syndrome (23.53%) and initially presenting nephrotic syndrome (23.53%).
- Hemophilia (42.84%) was the commonest cause of thrombocytosis amongst hematological diseases.
- Henoch schonlein purpura (40%) was the commonest cause of thrombocytosis amongst systemic diseases.
- Septicemia (69.24%) was the commonest cause of thrombocytosis amongst infective disorders.

Distribution of study subjects according to type of Thrombocytosis

Type of Thrombocytosis	No. of cases	%
Primary	1	0.66
Secondary	151	99.34
Total	152	100

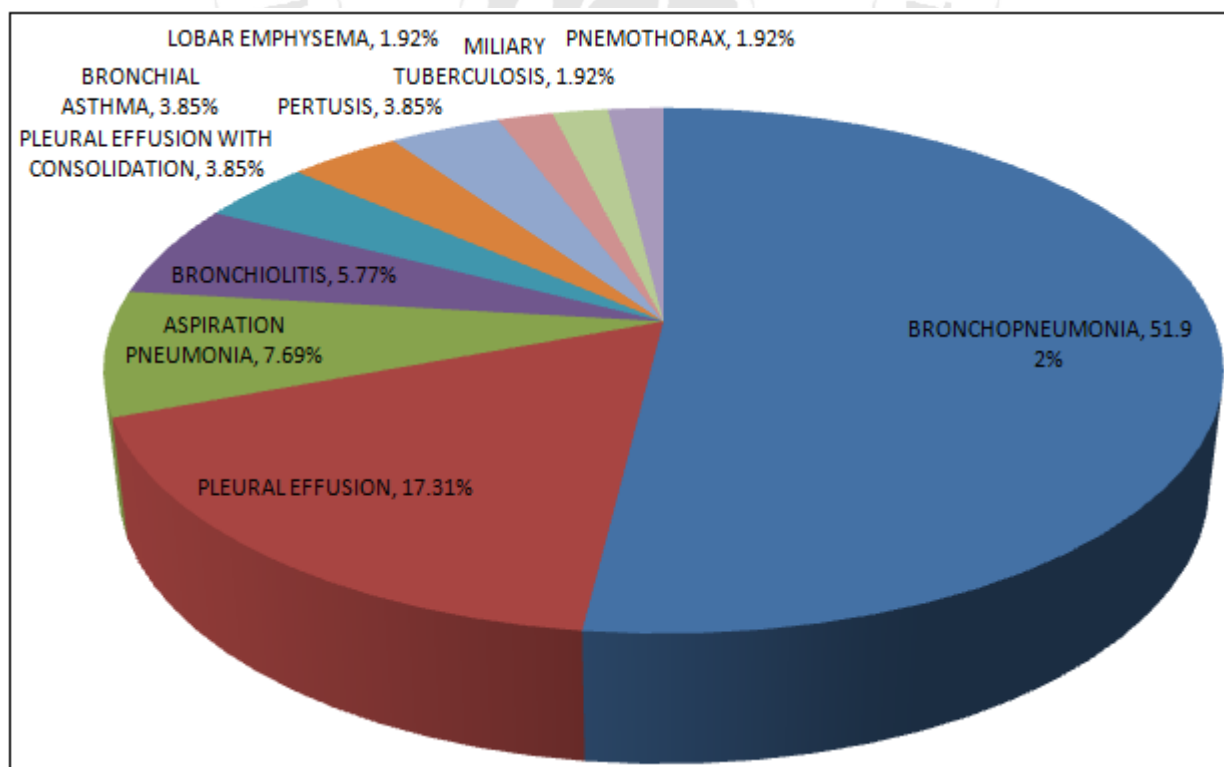
System Wise Distribution of Secondary Thrombocytosis Cases

System	No. of cases & %
Respiratory System	52 (34.44%)
Gastro-Intestinal System	33 (21.85%)
Central Nervous System	23 (15.23%)
Renal System	18 (11.92%)
Infection	12 (7.95%)
Hematological System	6(3.97%)
Systemic Disease	5 (3.32%)
Endocrine System	1 (0.66%)
Biotinidase Deficience	1 (0.66%)
Total	151 (100%)



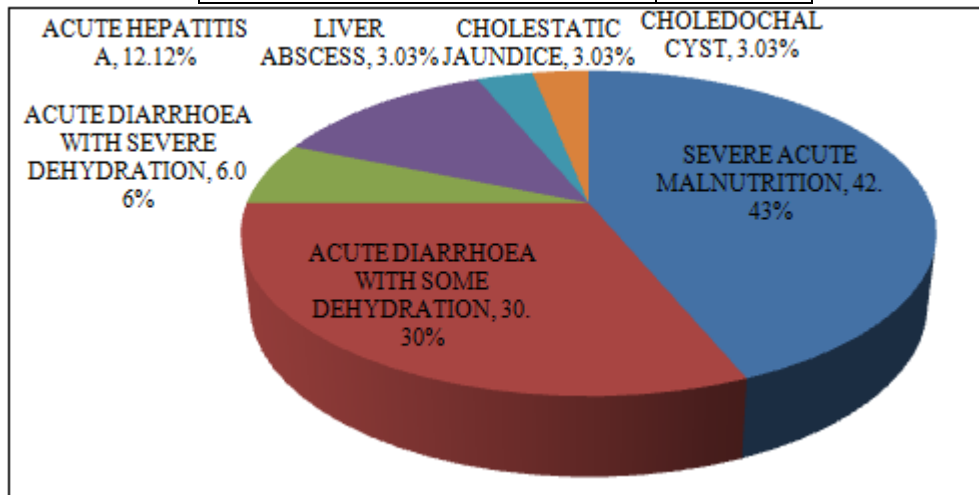
Disease Wise Distribution of Secondary Thrombocytosis in Respiratory System

Disease	No. of cases & %
BRONCHOPNEUMONIA	27 (51.92%)
PLEURAL EFFUSION	9 (17.31%)
ASPIRATION PNEUMONIA	4 (7.69%)
BRONCHIOLITIS	3 (5.77%)
PLEURAL EFFUSION WITH CONSOLIDATION	2 (3.85%)
BRONCHIAL ASTHMA	2 (3.85%)
PERTUSIS	2 (3.85%)
LOBAR EMPHYSEMA	1 (1.92%)
MILIARY TUBERCULOSIS	1 (1.92%)
PNEMOTHORAX	1 (1.92%)
TOTAL	52 (100%)



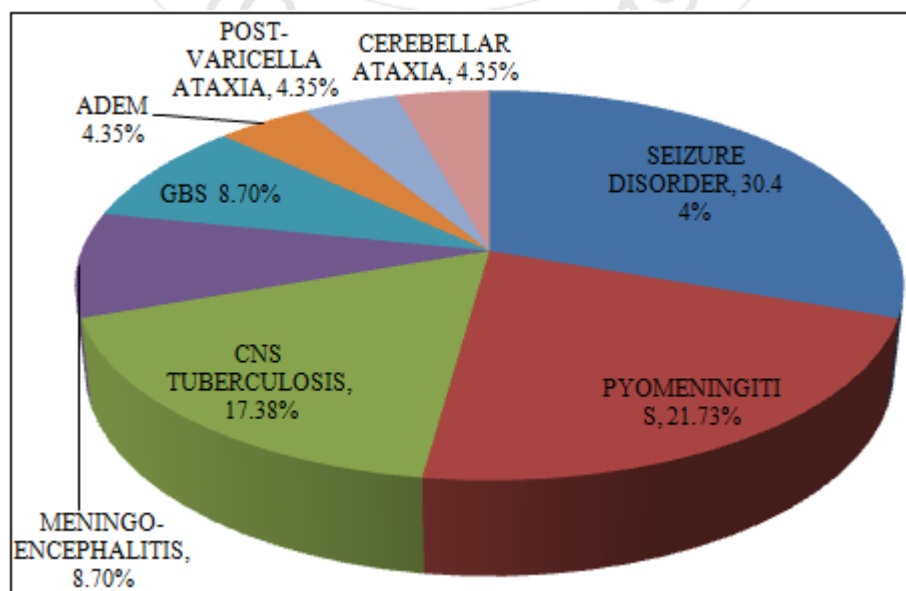
Disease Wise Distribution of Secondary Thrombocytosis in Gastro-Intestinal System

Disease	No. of cases & %
Severe Acute Malnutrition	14 (42.43%)
Acute Diarrhoea With Some Dehydration	10 (30.30%)
Acute Diarrhoea With Severe Dehydration	2 (6.06%)
Acute Hepatitis A	4 (12.12%)
Liver Abscess	1 (3.03%)
Cholestatic Jaundice	1 (3.03%)
Choledochal Cyst	1 (3.03%)
TOTAL	33 (100%)



Disease Wise Distribution of Secondary Thrombocytosis in Central Nervous System

Diseases	No. of cases & %
Seizure Disorder	7 (30.44%)
Pyomeningitis	5 (21.73%)
Cns Tuberculosis	4 (17.38%)
Meningo-Encephalitis	2 (8.70%)
GBS (Gulliane-Barrie Syndrome)	2 (8.70%)
ADEM (Acute Demyelinating Encephalo-Myelitis)	1 (4.35%)
Post-Varicella Ataxia	1 (4.35%)
Cerebellar Ataxia	1 (4.35%)
Total	23 (100%)



4. Discussion

- The present study was conducted in SPMCHI, Department of Pediatrics, attached to SMS Medical College, Jaipur to find out the etiological and epidemiological factors associated with thrombocytosis.
- In the present study, males having thrombocytosis were 67.11% and females were 32.89% with male to female ratio being 2.04:1. Relatively larger number of workers (Chen HL et al, Serpil Duzgan et al, Nathiya Subramaniam et al, Jinn Li Wang et al, Celal Ozcan et al and Ka Wah Chan et al) has shown male preponderance.^{6,7,8,9,10}
- **Distribution of study subjects according to type of thrombocytosis:-** In our study, out of total 152 children with thrombocytosis, 151 (99.34%) children have secondary thrombocytosis and only 1 (0.66%) child has primary thrombocytosis. In conclusion, almost all thrombocytosis cases were having secondary thrombocytosis (reactive). Similar to our study result Nathiya Subramaniam et al had found most children having reactive thrombocytosis (99.8%) while in studies done by other workers (M.Griesshammer, M.Bangerter et al, Mehri Tafazzoli et al) reactive thrombocytosis observed in different proportion.^{5,9}
- **Distribution of thrombocytosis on the basis of system wise etiology:-** Out of 152 children, 1 (0.66%) child had primary and 151 (99.34%) children had secondary thrombocytosis. The causes of secondary thrombocytosis was respiratory disease were 52 (34.44%), gastro-intestinal diseases were 33 (21.85%), nervous system diseases were 23 (15.23%), renal diseases were 18 (11.92%), infective diseases were 12 (7.95%), hematological diseases were 6 (3.97%), systemic diseases were 5 (3.32%), endocrine disease (diabetes mellitus) was 1 (0.66%) and biotinidase enzyme deficiency was 1 (0.66%). Respiratory disease was the commonest cause of secondary thrombocytosis in children.
- Similar to our study result following workers (Vora AJ, Lilleyman JS et al, Chen HL, Chiou SS et al, Hsiu-Lin Chen et al and Jinn-Li Wang et al) had found respiratory system diseases as the commonest cause for reactive thrombocytosis^{7,11,12}. While other workers (M.Griesshammer, M.Bangerter et al, Mehri Tafazzoli et al, Celal Özcan and Tülin Revide Şaylı et al) observed different system diseases as to be the commonest cause of thrombocytosis^{3,4,5}.
- **Distribution of secondary thrombocytosis in respiratory diseases:-** Most common cause of secondary thrombocytosis was respiratory disease (34.21%). Amongst respiratory diseases, bronchopneumonia were 27 (51.92%), pleural effusion were 9 (17.31%), aspiration pneumonia were 4 (7.69%), bronchiolitis were 3 (5.77%), pleural effusion with consolidation were 2 (3.85%) and others were 7 (13.46%). So, bronchopneumonia was the most common cause of thrombocytosis amongst patients with respiratory tract infections followed by pleural effusion. Similar observation have made by Wolach B, Morag H et al and Vora AJ, Lilleyman JS et al where bronchopneumonia as commonest cause in respiratory disease.^{10,11}

- **Distribution of secondary thrombocytosis in gastro intestinal diseases:** In our study, severe acute malnutrition (SAM) was the most common cause of thrombocytosis among patients with gastro-intestinal tract infections. Similar to our results following workers (Vora AJ, Lilleyman JS et al, M.Griesshammer, M.Bangerter et al, Jinn-Li Wang et al and Celal Özcan and Tülin Revide Şaylı et al) have also reported gastrointestinal disease as second most common cause of thrombocytosis^{4,5,10,11}
- **Distribution of secondary thrombocytosis in central nervous system diseases:-** In our study among central nervous system disorders seizure disorders (30.44%) followed by pyomeningitis (21.73%) were the two most common cause of thrombocytosis. Ka Wah Chan et al and Vora AJ, Lilleyman JS et al have reported pyomeningitis as commonest cause and Jinn-Li Wang et al have observed seizure disorder as most common cause of thrombocytosis, by enlarge their study results are similar to present study results.^{8,10,11}

5. Recommendations and Suggestions

- 1) Although thrombocytopenia in a patient is given more attention than thrombocytosis. It is a time when all clinician have started thinking over thrombocytosis and it's clinical implications. Though this study we have made an attempt to study the etiological factors of thrombocytosis and it's severity.
- 2) On the basis of this study following suggestions and recommendations are made-
- 3) We recommend more studies with larger number of subjects falling in both primary as well as secondary thrombocytosis.
- 4) Further studies with larger number of subjects are also required to studies severity of thrombocytosis, various etiological factors and system wise factors and their association with severity.

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