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Study of Reactive Thrombocytosis in Children

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Abstract:- Thrombocytosis, or elevations of platelet count in the peripheral blood to values >400,000/mm3, is common in infancy and childhood, occurring in 3-13% of children. Primary thrombocytosis is divided into familial & essential thrombocytosis, while reactive thrombocytosis occurs frequently. Most of the available studies on the thrombocytosis in children are from developed countries, and there appears to be geographical variations in causes of reactive thrombocytosis (RT). The present study was undertaken to ascertain common etiology of reactive thrombocytosis, to assist the general pediatrician in dealing with this common hematological finding in everyday clinical practice. This study was conducted on 100 inpatients admitted under the department of pediatrics, Manipal hospital, Bangalore from August 2011 to July 2012. Consecutive children of both sexes up to the age of 5 years, having thrombocytosis (platelet count > 4,00,000/mm3) were enrolled. An appropriate EDTA blood sample was collected at admission and platelet counts were analysed by automated analyser (Beckman coulter 780) and reconfirmed by manual method. Relevant investigations were done according to the clinical history and physical findings, to establish the diagnosis. Age, sex and varied diagnosis were correlated with the thrombocytosis and results were analysed. Reactive thrombocytosis is a very common observed condition in children, unlike primary thrombocytosis which is rare. Most of the literature is from the western world, and this study was conducted to know the common etiologies responsible for reactive thrombocytosis in this part of the country. In most children with reactive thrombocytosis, platelet counts are modestly elevated up to 700,

***Keywords*:-** *Thrombocytosis, Platelet Count, Hematology, Children, Blood Sample*

I. INTRODUCTION

Thrombocytosis or elevations of platelet count in the peripheral blood to values >400,000/mm^3 is common in infancy and childhood, occurring in 3-13% of children[1]. Thrombocytosis is classified according to its origin into primary and secondary (reactive). Primary is divided into familial & essential thrombocytosis. Essential thrombocytosis is very rare in childhood however, reactive thrombocytosis occurs frequently. While in older adults an elevated platelet count can signify an underlying hematological disease, in children almost every case with elevated platelet count is due to another medical condition such as infection, chronic inflammation, collagen vascular and renal diseases, Langerhan's cell histiocytosis, iron deficiency, hemolytic anemia and Kawasaki disease (KD). Drugs are other less frequent causes of secondary thrombocytosis in children.

Pediatricians are commonly puzzled in cases of thrombocytosis to determine the underlying cause and the need for therapy. Most of the available studies on the thrombocytosis in children are from developed countries. There appears to be geographical variations in causes of reactive thrombocytosis (RT), as Kawasaki disease was reported as a common cause of thrombocytosis in a study from Japan[2], though it was not replicated in other studies[3-5]. Therefore, it is probable that spectrum of causes may be different in India compared to developed countries. There is paucity of Indian literature on thrombocytosis, hence the present study was undertaken to ascertain common etiology of reactive thrombocytosis, to assist the general pediatrician in our part of country in dealing with this common hematological finding in every day clinical practice.

II. PATIENTS AND METHODS

It is a prospective correlation study of 100 inpatients admitted under the department of pediatrics, Manipal hospital, Bangalore from August 2011 to July 2012. Consecutive children of both sexes up to the age of 5 years, having thrombocytosis (platelet count > 4,00,000/mm^3) were enrolled in the study. An appropriate EDTA blood sample was collected at admission and platelet counts were analysed by automated analyser (Beckman coulter 780) and reconfirmed by manual method. Relevant investigations were done according to the clinical history and physical findings, to establish the diagnosis. Age, sex and varied diagnosis were correlated with the thrombocytosis and results were analysed. Ethical committee approval was taken for the study.

- *Inclusion criteria*

Hospitalised children between 6months to 5 years age group, with elevated platelet count (>4,00,000/mm^3)

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➢ *Exclusion criteria*

Primary thrombocytosis.

III. RESULTS

➢ *Age distribution*

Six months to 5 year age group children were selected for the study. Majority of children (44%) were in the age group of 6 months to 1 year, followed by the group 1year to 2 year (27%). As the age advances, incidence of reactive thrombocytopenia cases decreased (Table 1, Figure 1). Median age group in our study was 1.4 years.

Table1 Distribution According To Age

Age	No. of cases
6months- 1 year	44
1 – 2year	27
2 – 3year	14
3 – 4year	10
4 – 5 year	05

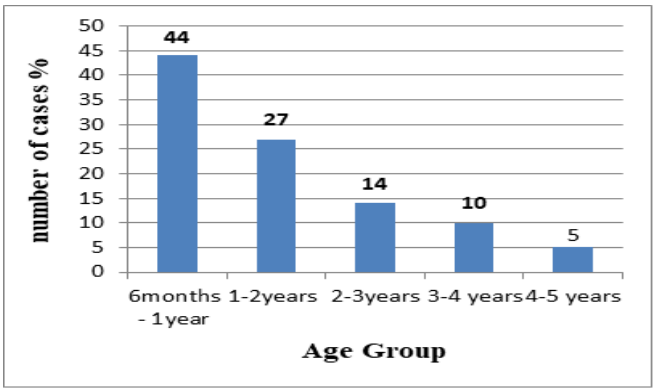

Fig1 Distribution According To Age

➢ *Sex distribution*

Among 100 children analysed, 53 were males and 47 were females (Table 2, Figure 2)

Table 2 Distribution According To Sex

Sex	No. of children
Males	53
Females	47
Total	100

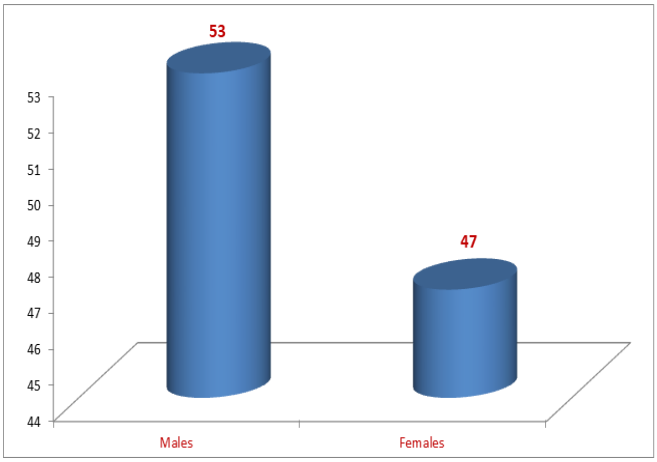

Fig 2 Distribution According To Sex

➢ *Range of Thrombocytosis*

Platelet count more than 4,00,000/mm^3 was taken as cut-off value to include in the study. Majority of the cases (92%) had mild thrombocytosis in the range of 4-7 lacs. Moderate thrombocytosis (platelets between 7-10 lacs) were observed in 6% of children while extreme elevations (platelet count > 10 lacs) were seen in only 2% of children with reactive thrombocytosis (Table 3, Figure 3). Average platelet count in our study was 5.39 lacs/cmm (median 5.16 lacs/cmm) and it was ranging from 4.02 lacs to 10.08 lacs/cmm.

Table 3 Range Of Thrombocytosis

Platelet count	No. of patients
4,00,000 to 7,00,000/cmm	92
7,00,000 to 10,00,000/cmm	06
>10,00,000/cmm	02

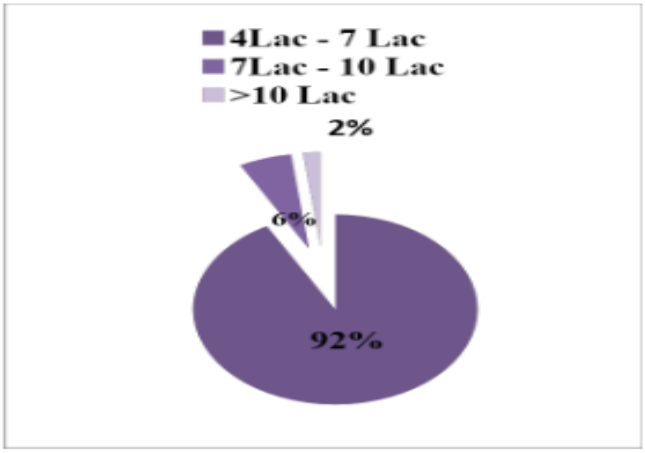

Fig 3 Range of thrombocytosis

➢ *Causes Related to Respiratory System*

Infection of the respiratory tract remained the most common cause of reactive thrombocytosis among the 100 children evaluated at our institute (Table 4, Figure 4). Lower respiratory tract infections were majority in number (33%), with pneumonia being the common cause (20%). Upper respiratory infections were less in number (5%).

Table 4 Respiratory Tract Causes

Upper respiratory and ENT	Pharyngitis	02
	Scarlet fever	01
	Pertusis	01
	AOM	01
Total – 05		
Lower respiratory	Bronchopneumonia	12
	Bronchiolitis	03
	WALRI	04
	Lobar pneumonia	08
	Empyema	01
	FB with pneumothorax	01
	H1N1with ARDS	01
	Aspiration pneumonia	03
Total- 33		
TOTAL: 38		

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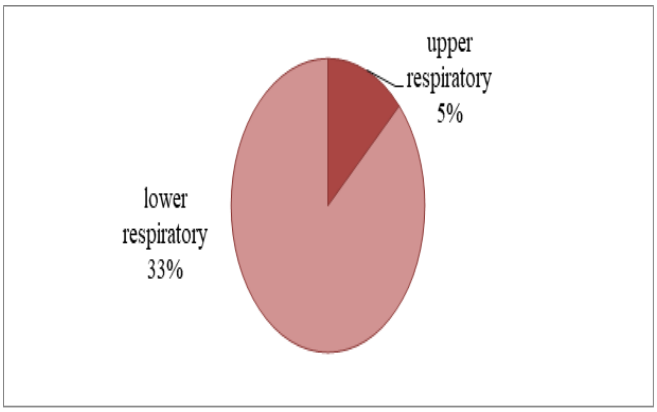

Fig 4 Respiratory Tract Causes

➢ *Causes related to Gastrointestinal System*

Gastrointestinal tract related causes were responsible for 13% of reactive thrombocytosis. Among them viral diarrhea was the commonest cause (6%) and most of the children presented had associated moderate dehydration.

Table 5 Gastrointestinal TRACT CAUSES

Cause	No. of cases
Infective diarrhea	02
Viral diarrhoea	06
Enterocolitis	01
HUS	01
Persistant diarrhea	01
Appendicitis	01
Intestinal obstruction	01
Total	13

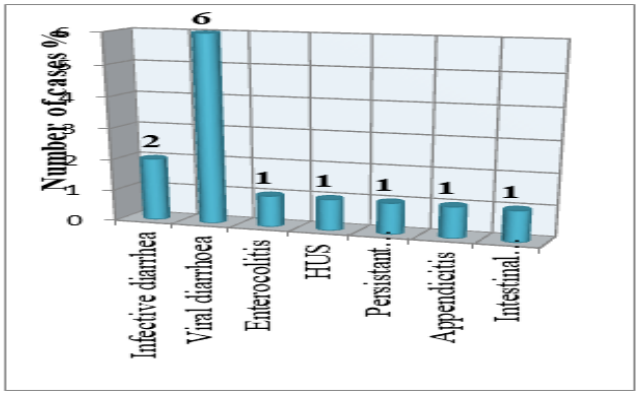

Fig 5 Gastrointestinal Tract Causes

➢ *Causes Related to Genitourinary System*

Reactive thrombocytosis was also common in conditions related to genito-urinary system (Table 6, Figure 6). Majority of the cases were due to urinary tract infection (9%). Acute glomerulonephritis and renal calculi were seen in one patient each.

Table 6 Genito-Urinary Causes

Cause	No. of cases
UTI	08
Nephrotic syndrome	04
Renal calculi	01
AGN	01
Total	14

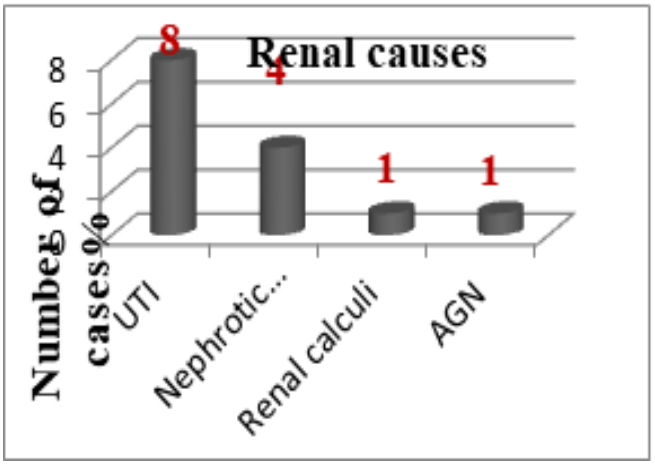

Fig 6 Genito-Urinary Causes

➢ *Causes Related to Central Nervous System*

Infectious conditions were predominant among the causes related to central nervous system, accounting to 70% of cases in total 10 cases. Febrile seizure secondary to viral fever was the most often cause. Non-infectious conditions like seizure disorder and GB syndrome also have contributed to reactive thrombocytosis in few cases.

Table 7 Central NERVOUS SYSTEM RELATED CAUSES

Cause	No. of cases
Febrile Seizures	05
Seizure disorder	02
Pyogenic meningitis	01
GBS	01
TB meningitis (disseminated)	01
Total	10

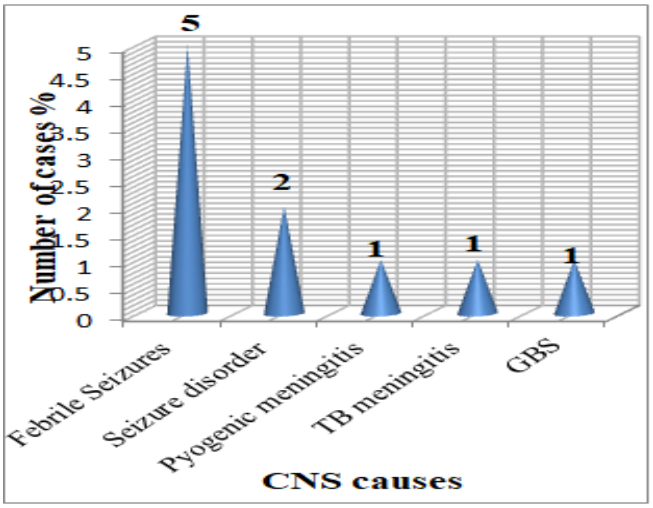

Fig 7 Central Nervous System Related Causes

➢ *Other Systemic Causes*

Reactive thrombocytosis is also seen in many conditions where definite localization is not present. It includes common etiology like infection to rare causes like Langerhan's cell histiocytosis (LCH). Staphylococcal scalded skin syndrome (SSSS) and urticaria were the cause of reactive thrombocytosis in 2 cases each. One child with kerosene ingestion also had elevated platelet count due to presence of tissue damage.

ISSN No:-2456-2165

Table 8 Other Systemic Causes Associated

Condition	No. of cases
Enteric fever	01
Sepsis	03
SSSS	02
Urticaria	02
Rickettsial	01
LCH	01
PUO	02
Viral fever	02
kerosene ingestion	01
Total	15

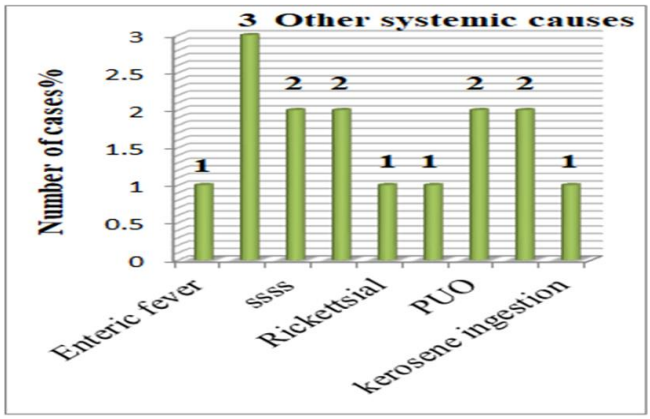

Fig 8 Other Systemic Causes Associated

➢ *Kawasaki disease*

Kawasaki disease (KD) was the cause of reactive thrombocytosis in 6 children. Three cases were incomplete KD and all cases were below 2 years of age.

➢ *Localised abscess*

Reactive thrombocytosis was seen one each case of lymph node abscess and gluteal abscess.

➢ *Tumors*

One each case of adrenal adenoma and pilocytic astrocytoma had reactive thrombocytosis

➢ *Comprehensive Assessment*

Reactive thrombocytosis occurred in varied conditions afflicting almost every part of the body (Table 9, Figure 8). Respiratory conditions were the commonest cause (38%), followed by genito-urinary (14%) and gastrointestinal (13%) conditions. Tumors were among the rare cause of reactive thrombocytosis in our series.

Table 9 Comprehensive Distribution of Causes

Sl No.	System	No. of cases
1	Respiratory	38
2	GIT	13
3	Genitourinary	14
4	CNS	10
5	Other systemic	15
6	Rheumatic disease	06
7	Tumors	02
8	Local abscess	02

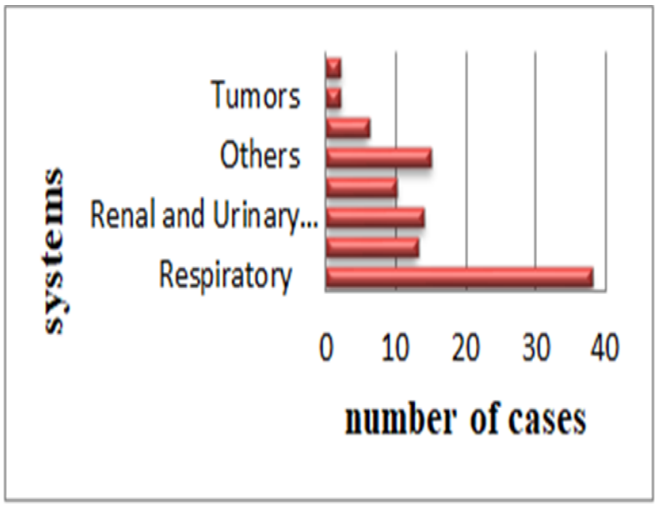

Fig 8 Comprehensive Distribution of Causes

➢ *Infectious versus non-infectious etiology of reactive thrombocytosis*

Infectious conditions were the most common cause of reactive thrombocytosis, accounting to 76% in our series. Non-infectious conditions attributed to only 24% (Figure 9).

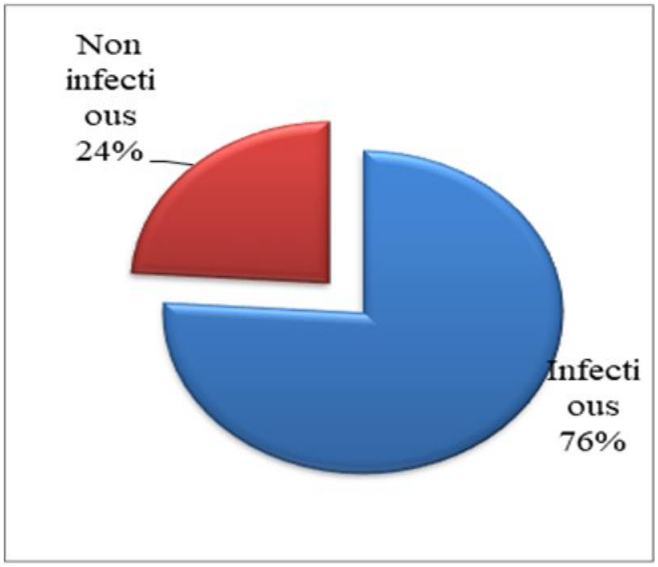

Fig 9 Infectious Vs Non-Infectious Causes

IV. DISCUSSION

Reactive thrombocytosis is a very common observed condition in children, unlike primary thrombocytosis which is rare. Availability of automated hematology analyzers gives results of platelet counts as a part of the routine hematology work-up, with a dependable degree of accuracy. When found, however, it poses diagnostic dilemma of its importance. Few times, it is a marker of subclinical underlying conditions. From various published series, it is known to affect up to 15% of hospitalized children.[1,4-8]Most of the literature is from the western world, and so we conducted this prospective study on in-patients of our tertiary referral centre to know the common etiologies responsible for reactive thrombocytosis in this part of the country.

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In our series we found 71% of reactive thrombocytosis cases within 2 years of age, among which 44% were below one year of age. Mantadakis et al also reported it to be more common in neonates, particularly premature ones, and infants up to 2 years of age and less common in older children.[52] Dinesh Yadav et al reported similar findings with < 2 year children contributing to 60% of total cases.[53] Male to female ratio in our study was similar with slight increase in male children (1.12:1). But Yadav et al reported males contributing more than half of cases (64% vs 36%). In most children with reactive thrombocytosis, platelet counts are modestly elevated up to 700,000/µL. Moderate thrombocytosis (platelets between 700,000 and 1,000,000/µL) occur in 6-8% of children with reactive thrombocytosis, while platelets >1,000,000/µL occur in less than 2-3% of children with reactive thrombocytosis.[7] Even in our series we had the similar range of elevation in platelet count in accordance with literature.

Varied conditions cause elevations in platelet count and respiratory infection accounted for majority of cases of reactive thrombocytosis. Lower respiratory tract infections were the common cause among this, accounting to 86.84% among all respiratory causes in our series. In one study, thrombocytosis occurred in about 40% of children with lower respiratory tract infection due to mycoplasma pneumonia.[11] In our series, 60.52% of respiratory causes were due to pneumonia. Thrombocytic patients with pneumonia may have a more severe clinical course, although this is questioned.[9]

Causes related to gastrointestinal (GI) system were most often due to infectious etiology. In our series infections contributed to 62.5% of GI causes. Many series in the literature have reported similar findings.[7,8,27] The presence of moderate dehydration will also contribute to raised platelet count when children present with diarrhea. One case of intestinal obstruction presented with thrombocytosis probably because of tissue trauma from distensive pressure.

Reactive thrombocytosis is also common in urinary tract infection. In our series, infection contributed to 64.28% of genito-urinary causes of elevated platelet count. Most of our cases had lower urinary tract infection. But Garoufi et al noted 74% of children with upper versus 14% with lower urinary tract infection presenting with reactive thrombocytosis in their series.[13] Hence, there is a variation in our presentation.

Infections of central nervous system, particularly bacterial meningitis due to Hemophilus influenza was one of the most common cause of reactive thrombocytosis before 1980s.[27-29]

Now its incidence has come down and respiratory infection is the commonest cause. In our series infections of central nervous system contributed to 7% of total reactive thrombocytosis cases. One study assessed the development of reactive thrombocytosis in 311 children with cerebrospinal fluid culture-positive bacterial meningitis. thrombo-cytosis was seen in 49% of the patients after the first week of treatment. Platelet counts were higher in infants and in patients with long duration of illness prior to admission. Subdural effusion and antibiotic therapy were associated with more pronounced thrombocytosis.[29]

We had only one case of tubercular meningitis with reactive thrombocytosis. Tubercular infection has not been reported to be a cause of reactive thrombocytosis, except in a study from Saudi Arabia.[27] But Yadav et al[53] reported its association in 4.5% of reactive thrombocytosis, possibly representing higher prevalence of tuberculosis in our subcontinent.

Reactive thrombocytosis is also seen in many conditions where definite localization is not present. We had two cases of pyrexia of unknown origin where site of infection could not be defined. Sepsis, staphylococcal scalded skin syndrome (SSSS) and rickettsial infection were among the causes contributing to reactive thrombocytosis. Enteric fever is known to cause decrease in platelet count, but it also present occasionally with thrombocytopenia as detected in our series. Kerosene ingestion, trauma, burns and any kind of tissue injury can cause reactive thrombocytosis. Langerhans cell histiocytosis (LCH), a disease with unpredictable clinical reactivations is also associated with thrombocytosis and platelet count is an indicator of disease activity in LCH.[22] Two children with localised abscess had reactive thrombocytosis as expected because of infection.

We had 6 cases of Kawasaki disease associated with reactive thrombocytosis. Thrombocytosis typically occurs in the second week of illness, and it is therefore not helpful in making a timely diagnosis.[52] Moreover the absence of thrombocytosis during convalescence does not exclude the disease. Thrombopoietin (Tpo) in conjuction with IL-6 contributes to thrombocytosis of patients with Kawasaki disease.[52]

Malignancies are uncommon causes of reactive thrombocytosis in childhood. Solid tumors of the liver [23,33-36], neuroblastoma[36] and acute lymphoblastic leukemia[37] were associated. Other than male sex, no clinical or laboratory characteristics were clearly associate with thrombocytosis in these children. We had one each of adrenal adenoma and pilocytic astrocytoma cases and both were male patients of 1 year age.

When a comprehensive analyses was made of all the etiological factors leading to reactive thrombocytosis, respiratory system contributed to the maximum number of cases (38%), followed by genito-urinay (14%), gastrointestinal (13%) and central nervous system (10%). Many published series have reported infections of respiratory tract accounting for 60-80% of cases of secondary thrombocytosis in children,[5,7-12,27] followed by infections of the urinary[13] and gastrointestinal tract.[7,8,27] Infections, both bacterial and viral, are by far the most common cause of secondary thrombocytosis in childhood. In our series infectious causes contributed to 76% of cases. Various systemic infections were most common cause of reactive thrombocytosis in many previous series.[4,5,27,53]

Reactive thrombocytosis is usually a benign condition and platelet counts normalize rapidly with treatment of underlying etiology without causing any thromboembolic complications. No thromboembolic complications were observed in earlier pediatric series on thrombocytosis even in cases with severe and extreme thrombocytosis, suggesting that no active intervention is required for thrombocytosis in these children. However, patients having underlying iron deficiency state or other prothrombotic factors (hyperhomocystinemia, nephrotic syndrome, active tuberculosis, cases with Acute Lymphoblastic Leukemia receiving L-asparginase therapy, antiphospholipids antibodies, inherited thrombophilia etc.) can have thromboembolic complications and these patients may require antithrombotic prophylaxis. There are reports of increased incidence of thrombotic complications in association with iron deficiency anemia with or without thrombocytosis.[54]

In our series, we had two children with extreme thrombocytosis, one of aspiration pneumonia and one of nephrotic syndrome, and they had no complications associated with thrombosis. Dame and Sutor had also suggested that individually tailored thrombosis prophylaxis should be considered in patients with reactive thrombocytosis, if additional thrombotic risk factors are present.[7]

Table 10 shows the etiologic factors of thrombocytosis in various pediatric series, in comparison to our study.

Table 10. Etiologic factors of thrombocytosis in various pediatric series

S No.	Study	N	Infections	Hematological Cause	Tissue Damage	Tumors	Otheretiological Factors
1	Yohannan et al (5) †	663	203(30.6%)	128(19.3%)	101(15.2%)	13(2%)	76(11.5%)
2	Heng et al(8) ††	135	105(78%)	4(3%)	-	7(5.2%)	-
3	Vora et al(4)	36	27(75%)	-	2(5.5%)	6(16.7%)	-
4	Chan et al(27)	100	37(37%)	22(22%)	21(21%)	-	10(10%)
5	**Our study**	**100**	**76(76%)**	**-**	**4(4%)**	**2(2%)**	**18(18%)**

- Definition of thrombocytosis: Yohannan, et al., >500,000 /µL; Heng, et al., >600,000/µL; Vora, et al., > 800,000/µL; Chan, et al., >900,000/µL.
- †In 98 (14.8%) additional cases the authors considered thrombocytosis to be a rebound phenomenon.
- †† 9 (6.7%) cases were due to Kawasaki's disease.

V. CONCLUSIONS

Children below 2 years, and especially infants present frequently with reactive thrombocytosis than the older age group children. There is very little variation in the male and female distribution. Majority of the elevations in platelet count were of mild degree and extreme thrombocytosis were seen in only 2%. Infections are by far the most common cause of secondary thrombocytosis in childhood. Among all the etiological factors leading to reactive thrombocytosis, respiratory system contributed to the maximum number of cases (38%), followed by genito-urinay, gastrointestinal and central nervous system. In the infections of respiratory tract, thrombocytosis is a common finding in lower respiratory tract infection, being particularly prominent with pneumonia. Tuberculosis is rare cause of reactive thrombocytosis. Kawasaki disease can present with reactive thrombocytosis in non-infectious etiology. Elevated platelet count, even when of extreme grade does not cause thromboembolic complications and do not require treatment.

RECOMMENDATIONS

- Children below 2 years of age with elevated platelet count, reactive thrombocytosis should be considered.
- Mild degree of elevations are common in children and should be considered as an indication of underlying pathology; most often of an infection.
- Lower respiratory and urinary tract infections should be considered among the common causes.
- Rare causes like Langerhans cell histiocytosis, Kawasaki disease can be considered a differential diagnosis.
- Tumors are very rare cause of reactive thrombocytosis in children.
- As complications are infrequent, routine treatment of reactive thrombocytosis is not recommended, even in extreme thrombocytosis. However large sample size studies with more number of extreme thrombocytosis and associated prothrombotic conditions needs further eval

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